

Environmental Tobacco Smoke
and
Heart Disease

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THIS ISSUE BINDER IS INTENDED TO PROVIDE A BASIC,
COMPREHENSIVE REVIEW OF THE SCIENTIFIC LITERATURE
REGARDING A SPECIFIC TOPIC ON ETS AND THE HEALTH OF
NONSMOKERS.

PRIMARY STUDIES AND REVIEWS HAVE BEEN HIGHLIGHTED
TO IDENTIFY (1) USEFUL OR HELPFUL INFORMATION (YELLOW
HIGHLIGHT) AND (2) ADVERSE RESULTS OR OPINIONS (BLUE
HIGHLIGHT).

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ETS and Heart Disease

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Introduction

This notebook discusses and provides copies of the public literature bearing on the claim that environmental tobacco smoke (ETS) is related to heart disease. The current notebook is an update, following its initial preparation in 1991.

Currently, there is a total of 12 epidemiological studies presenting data on a possible statistical association between ETS and heart disease incidence or mortality. These epidemiological reports are the primary basis for claims of an elevated heart disease risk in nonsmokers exposed to ETS. However, the literature also contains several laboratory and statistical reports dealing with ETS and exercise performance (particularly in angina patients), with biochemical factors suggested as involved in the development of heart disease or with atherosclerosis. These reports are also discussed and included in this notebook.

Each of the articles included in this notebook has been highlighted in blue and yellow. The blue highlighting identifies "adverse" comments -- that is, comments supporting a relationship of ETS with heart disease, or that otherwise express unfavorable data or opinions regarding tobacco. The yellow highlighting identifies "helpful" comments -- that is, comments that challenge, or at least that are concessionary concerning, the potential

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involvement of ETS or tobacco in disease causation. Letters to the editor or other editorial comments are included with several of the articles in this notebook.

The initial section of this notebook contains an overview and discussion of the literature. The literature itself is grouped into four appendices.

Appendix A (Tabs 1-14) contains the 12 epidemiological reports with data on a potential association between ETS and heart disease (Tabs 1-12). Appendix A also contains two epidemiological reports with data on other cardiovascular diseases -- namely stroke (Tab 13) and Buerger's disease (Tab 14). A summary and discussion of major criticisms is provided for each of the 12 ETS/heart disease studies.

Appendix B (Tabs 15-20) contains major meta-analyses and reviews concluding that ETS is associated with an elevated heart disease risk.

Appendix C (Tabs 21-34) contains opinions that the data are inadequate to conclude that ETS is related to heart disease.

Appendix D (Tabs 35-51) contains a mixed group of articles which provide data concerning ETS in relation to exercise

performance, potential effects in heart disease patients or in relation to biochemical and cellular processes, including atherosclerosis.

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Epidemiologic Reports and Reviews

Reports with original data

There are currently 12 studies presenting epidemiological data on a possible statistical association between ETS and heart disease incidence and mortality.

The ETS associated risks reported in the 12 epidemiological studies are summarized in the following table.

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Epidemiology

ETS/Heart Disease Relative Risks

	<u>Sex</u>	<u>Relative Risk</u>
Butler (1990) ¹	F	1.4
Dobson, et al. (1991) ²	M	.97
	F	2.46* (Home)
	M	.95
	F	.66 (Work)
Garland, et al. (1985) ³	F	2.7
He, et al. (1989) ⁴	F	1.5*
Helsing, et al. (1988) ⁵	M	1.3*
	F	1.2*
Hirayama (1984) ⁶	F	1.3
Hole, et al. (1989) ⁷	M+F	2.0*
Humble, et al. (1990) ⁸	F	1.6
Lee, et al. (1986) ⁹	M+F	1.0
Martin, et al. (1986) ¹⁰	F	3.4*
Palmer, et al. (1988) ¹¹	F	1.2
Svendsen, et al. (1987) ¹²	M	2.2

*Reported to be statistically significant at the 95% level of confidence.

Only five of the 12 epidemiological studies regarding ETS and heart disease report a statistically significant result at the 95% level of confidence. These are: (1) He, et al. (1989), a Chinese language report based on only 34 female heart disease patients; (2) Helsing, et al. (1988), a study based on a Maryland census in which the information regarding spousal smoking (used to estimate ETS exposure) was from 1963; (3) Hole, et al. (1989), a Scottish study based on only 84 heart disease deaths; (4) Martin, et al. (1988), a report based on only 23 women who reported having a heart attack and which was given at a conference but apparently not otherwise accepted for publication; and (5) Dobson, et al. (1991), an Australian study which reported an association with home exposure for women only and not at all for workplace exposure.

In sum, seven of the 12 studies of ETS exposure and heart disease have failed to report a statistically significant association. In the five studies that have claimed a statistically significant relationship, three were from outside the United States. Three were very small-scale. All of these studies suffer from a variety of serious methodological weaknesses.

In addition to the 12 ETS/heart disease reports, there is also an epidemiological (case-control) study reporting that spousal smoking was associated with increased stroke risk [relative risk of 1.7 (95% CI: 1.1-2.6)].¹³

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Epidemiological data have also been reported for ETS exposure in relation to Buerger's disease. Buerger's disease is an inflammatory condition leading to arterial occlusion in the peripheral vascular system. It has been reported to be statistically associated with cigarette smoking. Matsushita, et al.¹⁴ studied 40 Buerger's disease patients, in relation to smoking history and history of ETS exposure. Based on an examination of the progression or "aggravation" of the disease in these patients, the authors concluded that their results confirmed the relationship of "active" smoking with Buerger's disease, but that the "effects of passive smoking on the disease process were still inconclusive."

A list of the most common weaknesses in the epidemiological literature on ETS and cardiovascular disease is provided below. It will be recognized that these are characteristic of epidemiological studies of ETS in general, not simply those relating to heart and other cardiovascular diseases.

1. Small sample sizes.
2. Lack of statistical significance, or failure to test for statistical significance.
3. Potential misclassification of the smoking status of study participants.
4. Inadequate assessment of ETS exposure.

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5. Failure to control adequately for biases stemming from potential confounding variables.

6. Failure to confirm causes of death via autopsy or other histological methods.

Reviews claiming ETS-associated risk ("unfavorable" reviews)

Despite the scientific weaknesses in the epidemiologic literature on ETS and heart disease, several recent reviews have concluded that ETS is associated with an increased risk of heart disease and that, in fact, such exposure causes a large number of deaths each year. Each of these reviews attempted to estimate an overall risk based on the combined data from the epidemiologic studies. These estimated risk ratios are provided in the following table.

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Meta-Analyses and Reviews of ETS-Heart Disease Data

		<u>RR</u>
Wells (1988) ¹⁵	Males	1.31
	Females	1.23
Kawachi, et al. (1989) ¹⁶	<u>Home</u>	
	Males	1.3
	Females	1.2
	<u>Workplace</u>	
	Males	2.3
	Females	1.9
Kristensen (1989) ¹⁷	Both sexes	≈ 1.3
Glantz and Parmley (1991) ¹⁸	Both sexes	1.3
Steenland (1992) ¹⁹	Males	1.3
	Females	1.2

These estimates were generally derived from the statistical technique known as meta-analysis. Although these reviews varied somewhat in form, detail and focus, the estimates were generally similar, about 1.3, reflecting a 30% elevation in risk associated with ETS exposure.

The Kawachi, et al. (1989) discussion was fairly narrowly focused on New Zealand. The Kristensen (1989) discussion was a limited part of a larger discussion of factors involved in

cardiovascular diseases and the work environment. Thus, the major reviews were those by Wells in 1988, by Glantz and Parmley in 1991 and by Steenland in 1992. These three reports are discussed further below.

A. Judson Wells, a consultant to the American Lung Association, statistically combined the data from several reports on ETS and heart disease, including both prospective (cohort) and case-control studies. He then calculated overall relative risks (ETS exposed versus nonexposed) for lung cancer (1.44 for females; 2.1 for males), cancers other than lung (1.16 for females; no risk elevation for males) and heart disease (1.23 for females; 1.31 for males). Using various assumptions and statistical manipulations, Wells calculated numbers of ETS-related deaths for each disease category. He claimed that ETS exposure resulted in 46,000 deaths per year in nonsmokers. Of these, 3,000 are claimed to be from lung cancer. For cancers other than the lung, he calculated that ETS exposure results in 11,000 annual deaths. The largest number of deaths from ETS exposure was claimed to be due to heart disease. He claimed that 32,000 nonsmoker heart disease deaths per year stem from ETS exposure.

A more widely publicized review of ETS and heart disease was undertaken by two authors from the Department of Medicine, University of California, San Francisco. In their 1991 paper,

Stanton Glantz and William Parmley conclude that ETS exposure is statistically associated with an estimated 30% increase (relative risk of 1.3) in heart disease risk in nonsmokers. They argue, relying on Wells, that this translates into 37,000 heart disease deaths in nonsmokers stemming from ETS exposure. Glantz and Parmley also discuss a number of biochemical and experimental studies which purportedly support the biological plausibility of such a relationship.

In evaluating the claims by Wells and by Glantz and Parmley, it should be emphasized that meta-analysis, the technique from which they derive their risk estimates, is appropriately used only when the underlying studies are highly similar and of high quality. If the underlying studies are based on different populations and procedures and suffer from serious methodological weaknesses, then any meta-analysis will consequently be invalidated. These considerations are directly applicable to an evaluation of risk claims regarding ETS and heart disease. Wells (1988) and Glantz and Parmley (1991) base their claims on meta-analyses of a small group of epidemiological studies reporting a relationship between ETS exposure and an increased risk of heart disease. In general, these studies deal with spousal smoking and assess heart disease risk in the nonsmoking spouse. Otherwise, these studies used widely disparate methodologies, study populations and endpoints. Several are very weak, preliminary, available only in

abstract form, or are based on such scanty data that they quite arguably are not sufficiently reliable or valid even to be considered seriously in a meta-analysis.

Kyle Steenland, a National Institute for Occupational Safety and Health employee, also performed a risk assessment of ETS and heart disease. In a 1992 paper, he calculated that 35,000-40,000 annual U.S. heart disease deaths are attributable to ETS exposure. He concluded that "heart disease mortality is contributing the bulk of the public health burden imposed by passive smoking."

There were two important differences between Steenland's estimation process and that used by Wells, and later adopted by Glantz and Parmley. First, Steenland did not do a meta-analysis to obtain a pooled estimate of relative risk for heart disease mortality associated with ETS exposure. Instead, he simply adopted the relative risk reported in a single study of a Maryland sample (Helsing, et al., 1988; see endnote ref. 5) and applied that to the entire U.S. population. Second, he focused only on heart disease and did not attempt to calculate ETS-related deaths from other diseases.

Other than the above, Steenland's procedure for calculating deaths attributable to ETS exposure was generally

similar to that reported by Wells and by Glantz and Parmley. This estimation process involved: positing an overall increase in relative risk of heart disease associated with ETS exposure; making adjustments for potential misclassification and for background exposure; estimating the extent of exposure to ETS; and estimating the fraction of nonsmoker heart disease deaths attributable to ETS exposure. These estimates were incorporated into a formula using data on U.S. heart disease death rates and population estimates, from which was derived an estimated number of annual heart disease deaths attributed to ETS exposure. According to Steenland's calculations, "the overall estimate of ETS-attributable heart disease deaths for never-smokers and former smokers is 35000 to 40000." He further commented that these increased risks of death "are higher than those accepted in regulating environmental toxins."

In a 1992 position statement from the American Heart Association, it was concluded that ETS causes heart disease. (Taylor, et al.)²⁰

Reviews emphasizing inconclusiveness of the data ("favorable" reviews)

Reviews such as those by Wells, by Glantz and Parmley and by Steenland often receive a great deal of publicity. However, it is important to recognize that there have been a number of other

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examinations of the data concerning ETS and heart disease. Several important reviews have concluded that the data on this issue are equivocal and inadequate to support claims of an increased heart disease risk in nonsmokers exposed to ETS.

The first major reviews of the epidemiological data on ETS and heart disease appeared in 1986. In that year, a report of the United States Surgeon General²¹ examined the available data and judged that "no firm conclusion" (p. 10) could be made regarding a possible relationship between ETS and heart disease. Also in 1986, a similar evaluation appeared from a committee of the National Research Council of the National Academy of Sciences.²² This committee stated that any potential heart disease risk related to ETS would be "difficult to detect or estimate reliably" from epidemiological studies, and would be "the same order of magnitude as what might arise from expected residual confounding due to unmeasured covariates." (p. 263)

Thus, both the 1986 Surgeon General's Report and the National Research Council report judged that the data were insufficient to allow a conclusion that ETS exposure is a cause of heart disease. Even the 1991 review by Glantz and Parmley recognized this as a "reasonable" position, at least in 1986. On the other hand, Glantz and Parmley argued that data published since 1986 warrant that this conclusion be modified. However, other

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scientists have undertaken more balanced and critical reviews of the more recent data and have judged that it remains inconclusive. Several of the most significant of these recent reviews, and their conclusions, are as follows.

a. At a major conference on ETS held at McGill University in 1989, Lawrence Wexler, of the New York Medical College, concluded that recent data did not provide a basis for altering the earlier conclusions by the Surgeon General and National Research Council concerning ETS and cardiovascular disease.

Based on the available evidence, it is this author's opinion that it has not been demonstrated that exposure to ETS increases the risk of cardiovascular disease. (p. 139)²³

b. A similar evaluation was made by two scientists, D.F. Weetman and J. Munby, from the School of Pharmacology, Sunderland Polytechnic, Sunderland, United Kingdom. They presented their conclusions from a review of the literature on ETS and heart disease at an international conference on indoor air quality held in Lisbon, Portugal in April 1990.

It is concluded that no increased risk of cardiovascular disease can be associated unequivocally with exposure to ETS, and it seems probable that this will continue to be the case until specifically designed trials

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are instigated, and some objective measure of degree of exposure can be devised. (p. 215)²⁴

c. D.F. Weetman presented a similar conclusion at an indoor air quality conference in Bangkok, Thailand in November 1991.

It is concluded that too many important potentially confounding factors have been overlooked to decide if there is an association between exposure to ETS and cardiovascular diseases. (p. 275)²⁵

d. Another scientific review of this literature was performed by two physicians from the University of Munich, Germany and given at an international conference in Hungary in June 1990. The conclusion was similar.

Taking into account the small increase in coronary risk in passive smokers as compared to non-exposed subjects and also the low validity and small number of epidemiological studies available and the fact that their results are at least inconsistent, a relationship between passive smoking and cardiovascular diseases cannot be established on these data. (p. 6)²⁶

e. In a 1991 book discussing a wide range of issues involving ETS, the literature on heart disease was reviewed by Alan Armitage, former director of toxicology of a major European research laboratory and head of pharmacology at the

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Tobacco Research Council Laboratories in the United Kingdom. He judged that the scientific data have not established an increased heart disease risk in nonsmokers exposed to ETS.

It is clear that the evidence for a harmful effect of ETS in enhancing CHD [coronary heart disease] risk in non-smokers is not very convincing. . . . (p. 114)²⁷

f. In a subsequent review in 1993, Armitage, writing as a consultant pharmacologist and toxicologist, expressed a similar evaluation of the ETS/heart disease literature.

On the current evidence a causal relationship between exposure to ETS and the development of CHD has not been proved. (p. 27)²⁸

g. Armitage's 1993 review appeared in the Journal of Smoking-Related Diseases. In an editorial in the same journal issue, A.D.S. Caldwell, the journal's managing editor, emphasized that the issue of confounding variables was of particular importance in the case of heart disease. This is because of the hundreds of factors reportedly associated with the disease. Caldwell observed that the numerous heart disease risk factors make it extremely difficult to make confident statements about a potential role of ETS.

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But assessing the impact of ETS is an exercise made hazardous by confounding variables lurking around every statistical corner. In the case of CHD, for example, some 300 risk factors have at some time or other been identified--by what means is it possible to unravel these data and point the finger with any degree of confidence at ETS per se as a major causative element?²⁹

h. In 1991, Peter Lee, an independent British statistical consultant, published a critical analysis of the epidemiological literature relating to ETS exposure, cancer and heart disease. In the area of heart disease, he was particularly critical of the risk assessments by Wells (1988) and Kawachi, et al. (1989). Both of these risk assessments concluded that ETS is associated with a large number of heart disease deaths annually. Lee challenged this conclusion, and sided with the 1986 National Academy of Sciences and Surgeon General's reports, both of which had considered the ETS/heart disease data inadequate.

In the risk assessment by Wells, heart disease deaths formed 70% of the total. In that by Kawachi et al, they formed 89%. As noted above, in 1986 none of the major authorities considered that ETS had been shown to cause heart disease. Evidently Wells and Kawachi, in assuming that ETS causes heart disease, are jumping to a conclusion that a number of panels of distinguished scientists have not reached. While there are more data now than in 1986, it remains abundantly clear that the evidence still does not support this conclusion. (p. 199)³⁰

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i. In 1992, Peter Lee published a more detailed, book-length review of the epidemiological literature on ETS exposure in relation to mortality and several diseases. In his view, various weaknesses and biases in the data precluded the ability to draw any conclusion as to the potential association of ETS exposure and heart disease.

Mainly because of the problems caused by the strong likelihood of severe publication bias, it cannot be concluded from the existing evidence that ETS is associated with heart disease. The present author understands that the American Cancer Society intends to publish within the next year or so findings related to ETS based on its second large prospective study. It is hoped that results from its first prospective study will also be released. Until there is such evidence, and hopefully also evidence from other studies involving substantial numbers of deaths from heart disease with good control of confounding and with evidence on ETS exposure from sources other than the spouse or in the home, it is certainly premature to come to any conclusions. (pp. 145-196)³¹

j. In 1992, Domingo Aviado, M.D., a consultant with Atmospheric Health Sciences in Short Hills, N.J., published an extensive review of environmental tobacco smoke in the context of heart disease in the workplace. He did not consider the data supportive of an association of workplace ETS exposure with heart disease, and emphasized the low levels of ETS constituents to which workers might be exposed.

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It is the opinion of this author that the available studies do not support a judgment that ETS exposure is associated with any form of occupation-related heart disease. Although ETS reportedly contains constituents that have been associated with occupational heart disease, the concentrations are so low that it is unlikely for any substance to attain the corresponding TLV (threshold limit value) in a work environment. (pp. 475-476)³²

k. G. Crépat, a scientist at the University of Dijon, France, reviewed the literature relating to ETS exposure and heart disease, in a presentation at an international indoor air quality meeting in Athens, in April 1992. He concluded that the relative risks for ETS and heart disease reported in epidemiologic studies have probably been overestimated and are not explained by the available "physiobiochemical" data.

This suggests that mean RR [relative risk] of CHD due to ETS exposure calculated from available epidemiologic studies, has probably been overestimated as at the moment it cannot be explained by physiobiochemical changes caused by ETS in the body. (p. 440)³³

l. Carbon monoxide is one of the constituents of ETS. Sometimes proposed to play a role in heart disease. John Mennear, of the School of Pharmacy, Campbell University (North Carolina) reviewed the literature relating to carbon monoxide, ETS and cardiovascular disease. His 1993 review paper

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concluded that ETS has not been scientifically shown to cause or exacerbate heart disease. Any potential role of carbon monoxide in ETS was considered to be especially unlikely.

The role, if any, of environmental tobacco smoke (ETS) in the causation and/or exacerbation of cardiovascular disease remains to be proven and defined. . . . It is concluded that if ETS plays a role in the etiology of cardiovascular disease, it is most likely not mediated through carbon monoxide. (p. 77)³⁴

Laboratory and Biochemical Studies

There are several experimental and biochemical studies that have been cited in the literature as supporting an increase in heart disease risk stemming from ETS exposure. A few of these reports claim that ETS exposure adversely effects exercise capacity and that in the case of heart disease patients, this can lead to attacks of angina (heart pain). Other reports have attempted to demonstrate that ETS exposure adversely affects some aspect of cardiovascular function, such as blood clotting (platelet activity) or cholesterol levels, or that it affects the underlying disease process (atherosclerosis).

In the area of exercise performance, there are four studies. In one of these, a 1985 report by McMurray, et al.,³⁵ healthy subjects were used and ETS exposure was claimed to have an

adverse effect on exercise performance. Two other studies, one by Aronow (1978)³⁶ and the other by Khalfen and Klochkov (1987)³⁷ used angina patients. In somewhat similar study designs, both reports claimed that when heart disease patients were exposed to ETS, they were not able to exercise as long before experiencing angina. The credibility of the Aronow report has been widely challenged in the literature. The Khalfen and Klochkov report is a Russian language article about which relatively little is known. In the fourth exercise performance study, Leone, et al. compared the cardiac performance during exercise testing in healthy subjects versus myocardial infarction survivors, in relation to ETS exposure. The authors reported that ETS exposure was associated with a decrease in peak exercise capacity in the myocardial infarction survivors, but not in the healthy subjects. For both groups of subjects, ETS exposure was associated with longer times to recovery of pre-exercise heart rates. The authors concluded:

Cardiac response to the exercise is significantly worsened by passive smoke, especially in those subjects with previous myocardial infarction.³⁸

Regarding any of the exercise performance studies, whether with healthy or heart disease patients, a general criticism is that when dealing with ETS, it is almost impossible to "blind" either the experimenter or the subjects with regard to ETS exposure.

Thus, the possibility is always open that some subjective factor may influence the results.

There are very limited data attempting to demonstrate that ETS adversely affects some process that might be involved in blood clotting. The primary focus has been on the possibility that ETS may increase the tendency of certain blood components, known as platelets, to stick together. This claim has been made based mainly on data in four published reports. Three of these are from the same Austrian research group. (Sinzinger and Kefalides, 1982³⁹; Burghuber, et al., 1986⁴⁰; Sinzinger and Virgolini, 1989⁴¹) Of these three, one is merely a letter to the editor (Sinzinger and Kefalides, 1982) and another is a German language article with only an English abstract (Sinzinger and Virgolini, 1989). The fourth report, Davis, et al., (1989)⁴² is from a group of researchers in Kansas City, Missouri. It suffers from serious methodological weaknesses, particularly its failure to establish a proper control condition. [Platelet activity has also been assessed in an laboratory animal study involving exposure of rabbits to ETS, where the primary focus was on atherosclerosis. See Zhu, et al., 1993, endnote reference 50.]

There are three reports on children which assessed cholesterol and other blood components in relation to parental smoking status (Moskowitz, et al., 1990⁴³; Pomrehn, et al., 1990⁴⁴;

Feldman, et al., 1991⁴⁵), one of which (Pomrehn, et al., 1990) is only available as an abstract from a meeting presentation. These reports claimed that parental smoking was associated with decreases in HDL cholesterol, which some literature has argued may be associated with heart disease risk. A recent study from India made similar claims about adverse changes in adult cholesterol levels in relation to ETS exposure (Whig, et al.),⁴⁶ as did a report focusing on ETS exposure in the workplace. (White, et al.)⁴⁷

These cholesterol studies measured components of blood as the endpoint, but are essentially epidemiological studies in that they, at best, may suggest statistical correlations. As such, they suffer from weaknesses characteristic of other epidemiological studies of ETS exposure, especially difficulties in controlling for potential confounding variables and inadequate assessment of ETS exposure. Furthermore, the potential significance of blood values in relation to later heart disease risk, especially in groups of children, is highly speculative.

An abstract, from the Bowman Gray School of Medicine (Winston Salem, North Carolina), based on a presentation at a November 1991 American Heart Association meeting, reported that ETS exposure was associated with thickness of the walls of the carotid arteries. (Howard, et al., 1991)⁴⁸ The importance of carotid artery thickness is that it may be an indication of the

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severity of atherosclerotic involvement. Atherosclerosis of the carotid arteries is believed to underlie certain forms of stroke. These data were updated in a presentation at a March 1992 cardiovascular disease epidemiology conference, the abstract from which included information on some additional subjects, but otherwise reported similar results. (Howard, et al., 1992)⁴⁹

In an experimental report based on measurements in rabbits, tobacco smoke exposure reportedly led to increased levels of atherosclerosis. (Zhu, et al. 1993)⁵⁰ This is the first study to provide such experimental data. The study is subject to criticisms on the basis of questionable exposure protocols and other methodological weaknesses.

There have been limited data in the literature suggesting that certain vitamins might be a factor in the development of heart disease. Based on this theory, a 1992 meeting abstract measured dietary and plasma levels of vitamin C (ascorbic acid) in people exposed to ETS. Compared to a control group, ETS-exposed nonsmokers were reported to have decreased plasma levels and dietary intake of ascorbic acid. The authors concluded:

These results suggest that suboptimal AA [ascorbic acid] nutriture may contribute to increased heart disease risk associated with ETS exposure.⁵¹

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The significance of this report is highly questionable. Very few details are available -- not even the ages of the people studied are given in the abstract. In addition, the relationship, if any, of vitamin levels to subsequent heart disease is not scientifically established. Furthermore, even the authors acknowledge that their data on plasma vitamin C may at least in part be a result of different levels of dietary intake, rather than any direct effect of ETS exposure.

Some previous research involving active cigarette smokers has reported that smokers may have higher numbers of leukocytes (white blood cells) than nonsmokers. It has been speculated that these higher leukocyte counts may be one mechanism whereby smoking might increase heart disease risk. Green, et al. (1993)⁵² addressed the question of whether ETS-exposed nonsmokers might also show increased leukocyte counts.

Green, et al. examined a group of 250 male factory workers. These men were questioned regarding their smoking habits and their reported exposure to ETS in the workplace and at home. Urine samples were also collected for cotinine analysis. Green, et al. reported that, on the average, smokers had higher leukocyte counts compared with nonsmokers. However, based both on reported ETS exposure as well as on cotinine data, exposure to ETS was not associated with increased leukocyte counts. The authors concluded

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that, if ETS exposure is associated with increased heart disease risk, it is not mediated through an effect on leukocyte count.

These findings suggest that any association of passive smoking with coronary heart disease is not through an elevation of leucocyte count.
(Abstract, p. 14)

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Butler, T., "The Relationship of Passive Smoking to Various Health Outcomes Among Seventh-Day Adventists in California," Presented at the Seventh World Conference on Tobacco and Health, Abstract, 1990.

This report is an abstract from a 1990 conference presentation. The study involved a group of California Seventh Day Adventists who were followed from 1976 to 1982. Nonsmoking women were classified according to their husband's smoking status. The relative risk for fatal ischemic heart disease for women married to smokers was reported to be 1.4 (not statistically significant).

Risk ratios were also reported for lung cancer, all "smoking related" cancers, cervical cancer and all cancers. Confidence intervals were quite large, indicating no statistical significance for these values. However, for cervical cancer, a relative risk of 4.86 had confidence intervals indicating statistical significance.

Criticisms

1. This is an abstract only, apparently otherwise unpublished and not subject to peer review.

2. There are insufficient details to evaluate this study. For example, the abstract does not contain information on the number of nonsmoking women married to smokers versus those married to nonsmokers. Neither was data reported concerning the

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number of deaths, either overall or for any of the individual causes, on which the relative risks were based.

3. There was no reported statistically significant relationship between ischemic heart disease mortality and marriage to a smoker. The author admits that the study was flawed because of the small number of cases and the probable misclassification of passive smoking exposure, which "limited the ability to achieve conclusive results."

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THE RELATIONSHIP OF PASSIVE SMOKING TO VARIOUS HEALTH OUTCOMES AMONG SEVENTH-DAY ADVENTISTS IN CALIFORNIA.

Terrence F. Butler

Adventist Health Department, PO Box 14, Gordon, New South Wales, 2072 Australia

The relationship of passive smoking to the incidence of cancers, fatal ischemic heart disease and all natural cause mortality among Californian Seventh-day Adventists was investigated in 1988. From the 34,445 subjects of the Adventist Health Study cohort (1976-1982), two sub-groups were selected to evaluate the research questions. One, the spouse pairs cohort, consisted of 11,060 married couples. The second was a group of 6,467 subjects, referred to as the AHSMOG cohort, who were involved in a concurrent air pollution study. Follow-up for ascertainment of cancer incidence and mortality was from 1976 to 1982. Passive smoking exposure for the "spouse pairs" was based on the husband's smoking status in marriage. For the AHSMOG cohort Environmental Tobacco Smoke (ETS) exposure was based on the number of years lived with and the number of years worked with a smoker. For non-smoking females of the spouse pairs cohort, age-adjusted rate ratios and (95% C.I.) for each outcome represent those females married to a smoker compared to those females married to a non-smoker. Lung cancer RR = 2.01 (0.39-8.79), all smoking related cancers RR = 1.22 (0.61-2.44); cervical cancer RR = 4.86 (1.33-17.66) and all incident cancers RR = 1.20 (0.94-1.54). For females married to current smokers there was increased risk for fatal IHD, RR = 1.40 (0.51-3.84). No effect was observed for all natural cause mortality. For the AHSMOG cohort the results were less consistent by type of exposure measure and outcome. The small number of cases for some outcomes and the probable misclassification of passive smoking exposure limited the ability to achieve conclusive results. However, the results indicate an adverse effect for ETS exposure and are consistent with other reported results.

Presented at Seventh World Conference
on Tobacco and Health, 1990

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DOBSON, A.J., ALEXANDER, H.M., HELLER, R.F. AND LLOYD, D.M.,
"PASSIVE SMOKING AND THE RISK OF HEART ATTACK OR CORONARY DEATH,"
THE MEDICAL JOURNAL OF AUSTRALIA 154: 793-797, 1991

This article provides epidemiological data concerning a potential relationship between environmental tobacco smoke exposure and heart disease. All subjects were residents of the Hunter region of New South Wales, Australia. It used a case-control design. The cases were all individuals, male or female, within that region who experienced a "fatal or non-fatal definite or possible myocardial infarction or a coronary death." The controls were a sample comprising individuals in this region who were participating in an ongoing risk factor prevalence study sponsored by the World Health Organization. Data were collected on certain demographic characteristics, medical history, cigarette smoking and ETS exposure at home and at work.

Odds ratios and 95% confidence intervals reported for heart disease risk associated with ETS exposure at home were 0.97 (0.50-1.86) for men and 2.46 (1.47-4.13) for women. For ETS exposure at work, the odds ratios and confidence intervals were 0.95 (0.51-1.78) for men and 0.66 (0.17-2.62) for women. The authors concluded that their study "confirms previous findings of elevated risk of heart attack or coronary death associated with passive smoking at home." (p. 797) However, they observed that the "odds ratios for passive smoking at work did not suggest increased risk." (p. 793)

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Based on other aspects of their study, the authors claimed that the data confirmed increased heart disease risk in "active" smokers as well as increased ETS-related heart disease risk in exsmokers. Also, levels of blood fibrinogen (a clotting factor) were evaluated in relation to reported ETS exposure. Increased levels of fibrinogen were suggested to be a marker of ETS-related heart disease risk.

The authors commented on a variety of sources of biases in their study, including potential effects of confounding. Despite their belief that their study supports an adverse effect of both smoking and ETS exposure, they conceded that: "On balance, the effects of bias and confounding could have led to overestimation of risks due to passive and active smoking." (p. 796)

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ORIGINAL ARTICLES

Passive smoking and the risk of heart attack or coronary death

Annette J Dobson, Hilary M Alexander, Richard F Heller and Deborah M Lloyd

Objectives: To estimate the prevalence of passive smoking in an Australian population, the magnitude of risk of myocardial infarction or coronary death associated with passive smoking and the extent to which fibrinogen concentrations might be affected by passive smoking.

Design: A population-based case-control study of myocardial infarction or coronary death and passive smoking, and measurement of fibrinogen in a random sample from the same population.

Setting and participants: Residents of the Lower Hunter Region of New South Wales aged 35-69 years in 1988-1989. Case subjects were all those who suffered myocardial infarction or coronary death. Control subjects were participants in a risk factor prevalence survey.

Outcome measures: Myocardial infarction or coronary death, defined by criteria of the WHO MONICA Project, and fibrinogen concentration (measured in controls only).

Results: Prevalence of passive smoking at home was 20% for male case subjects, 13% for male control subjects, 29% for female case subjects and 19% for female control subjects. The corresponding prevalence rates for passive smoking at work were 40%, 44%, 41% and 37%. Odds ratios of myocardial infarction or coronary death for active smokers compared with non-smokers were 4.70 (95% confidence interval [CI], 3.35-6.58) in women and 2.71 (95% CI, 2.07-3.53) in men. For women the odds ratios of myocardial infarction or coronary death for those exposed to passive smoking at home were 2.46 (95% CI, 1.47-4.13) among non-smokers and 1.48 (95% CI, 0.67-3.30) among ex-smokers. For men the odds ratios for passive smoking at home were 0.97 (95% CI, 0.50-1.86) for non-smokers and 1.78 (95% CI, 1.13-2.79) for ex-smokers. The odds ratios for passive smoking at work did not suggest increased risk. Fibrinogen concentrations were generally higher among people exposed to passive smoking at home or work

compared with those not exposed but were not as high as concentrations in active smokers.

Conclusions: Passive smoking increases the risk of coronary heart disease and increased fibrinogen concentration provides a marker of its effect.

(Med J Aust 1991; 154: 793-797)

It is well established that cigarette smoking increases the risk of ischaemic heart disease.^{1,2} There is also evidence that passive smoking is associated with increased risk.³⁻⁵ One of the mechanisms by which smoking acts is by increasing fibrinogen concentrations which in turn promote thrombogenesis.⁶⁻⁸ This effect may also occur with passive smoking.⁹

To investigate the relationship between passive smoking and ischaemic heart disease we conducted a population-based case-control study and a study of fibrinogen in a random sample from the same population. We wished to estimate the prevalence of passive smoking in an Australian community, to estimate the magnitude of risk of heart attack or coronary death associated with passive smoking and to investigate the extent to which fibrinogen concentrations might be affected by passive smoking.

Methods

The setting for this study is provided by the World Health Organization (WHO) MONICA Project which is monitoring trends and determinants of cardiovascular disease in well defined populations over 10 years. One of these populations is in the Hunter Region of New South Wales, Australia, covering the local government areas of Newcastle, Lake Macquarie, Cessnock, Maitland and Port Stephens.

Cases

The case subjects for this study were all residents of the study area aged 35-69 years who during the study period had a fatal or non-fatal definite or possible myocardial infarction or a coronary death (with insufficient information for more specific classification).

Diagnosis was made under the criteria of the WHO MONICA Project.¹⁰ The principle used was to register doubtful cases and subsequently to exclude from analyses those which did not meet the diagnostic criteria. Various quality control measures were used to check completeness of case ascertainment. These included comparisons with the hospital morbidity data system and official death records obtained from the Australian Bureau of Statistics.¹¹

The study period was from July 1, 1988, to October 31, 1989. For people who had more than one event during this period only data for the first event were included in the analyses presented here. In addition to the diagnostic information, data were collected on demographic characteristics, medical history, cigarette smoking and exposure to passive smoking at home and at work. Current smokers were not asked about their exposure to passive smoking. Surviving case subjects were interviewed by the study nurses while they were still in hospital (in this population almost all the people with a suspected heart attack who survive long enough are admitted to hospital). Most case subjects who died some days after admission to hospital had been similarly interviewed by the study nurses. For case subjects who died before hospitalisation, in the emergency room, or shortly after admission to the wards, information was obtained from medical records, if available, or by questionnaires mailed to relatives. Information about smoking behaviour was not obtainable for 34% of fatal cases and 4% of non-fatal cases; data on passive smoking were missing for about 15% of all cases.

Controls

Participants in the community-based risk factor prevalence study conducted as part of the WHO MONICA Project were control subjects for the case-control study and were also the subjects for the study of fibrinogen. The risk factor study was conducted in June-December 1988 and June-November 1989. A stratified random

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sample of the study population was selected from the Commonwealth Electoral Roll with the sampling fraction being greater for the older age strata. People chosen for the sample were invited to attend study centres to complete a self-administered questionnaire and to have physical measurements made and blood samples taken.

Extensive systems of reminders and follow-up were used to encourage participation. The response rate for full participation in the study for the age group 35–69 years was 63%. Some people who were unable to attend a study centre for the physical measurements and blood samples did, however, complete a brief questionnaire which covered demographic characteristics, smoking behaviour and medical history. Others were interviewed at home to obtain this information. Inclusion of data from all these people gives a response rate of 80% for this age group.

For comparisons of smoking behaviour among cases and controls, data for all the control subjects who participated fully in the risk factor survey or who only completed the brief questionnaire or who participated in home interviews were used to reduce non-response bias. Information on passive smoking, however, was only obtained from those who participated fully in the survey. As for case subjects, current smokers in the control group were not asked about their exposure to passive smoking.

Fibrinogen

Blood samples obtained from people who participated fully in the risk factor survey were assayed to determine fibrinogen concentrations. This was not done for case subjects because this was, of course, impossible for fatal cases and for non-fatal cases the concentration of fibrinogen in the blood could be affected by the myocardial infarction and treatment for some time after the event. Blood samples were anticoagulated immediately after collection with disodium edetate in commercially supplied tubes. Plasma fibrinogen was assayed by radioimmunoassay using commercially prepared plates (Behring, Germany) and Norpanigen Plasma Standard (Behring, Germany) as the standard.

Statistical analysis

Age, sex and a prior history of heart disease are important confounders of the relationship between risk of heart attack or coronary death and smoking, so the estimates from the case-control study were adjusted for these factors. The statistical program GLIM was used to calculate adjusted odds ratios and approximate confidence intervals by logistic regression.¹¹ Terms for age (five-year age groups from 35–39 to 64–69 years) and history (previous myocardial infarction or history of other ischaemic heart disease versus no history) and interaction between these two factors were included in the model as well as terms for the smoking variables.

Any relationship between passive smoking

and the risk of heart disease may be affected by the person's own smoking history and so results for non-smokers and ex-smokers were calculated separately. The program Epi-Info was used to calculate exact confidence intervals and tests for trend for crude odds ratios.¹²

Fibrinogen concentrations are approximately log-normally distributed and they increase with age and body mass index (kg/m^2). Therefore the logarithmic transformation was used and mean values for smoking groups were compared after adjustment for the covariates of age and body mass index. The procedure GLM of the SAS program was used.¹³ For presentation of the results, estimated mean concentrations (g/L) are given for persons aged 50 years with a body mass index of 25.

Results

Prevalence rates for passive smoking at home were higher among cases than controls and among women compared with men. Prevalence rates for passive smoking at work were around 40% for all groups (Table 1). Many of the participants in the study, particularly the case subjects, were retired or, especially among women, did

not work outside the home, so the numbers available for analysis of passive smoking at work were smaller than those for passive smoking at home.

For women the odds ratios for heart attack or coronary death for those exposed to passive smoking at home compared with those not exposed were 2.46 for non-smokers (95% confidence interval [CI], 1.47–4.13) and 1.48 for ex-smokers (95% CI, 0.67–3.30) after adjustment for age and history of heart disease. For men the corresponding adjusted odds ratios were 0.97 (95% CI, 0.50–1.86) for non-smokers and 1.78 (95% CI, 1.13–2.79) for ex-smokers (Table 2).

The odds ratios for passive smoking at work were not high and the confidence intervals were wide (Table 3).

To compare the magnitude of risk associated with passive smoking with risk associated with active smoking, adjusted odds ratios for current smokers and ex-smokers compared with non-smokers are shown in Table 4. There were consistent and statistically significant dose-related gradients with current smokers having the highest odds

TABLE 1: Prevalence of passive smoking at home and at work among cases and controls who did not themselves smoke

Age (years)	At home		At work	
	Cases	Controls*	Cases	Controls*
Men				
35–49	30%	10%	49%	34%
50–59	27%	18%	43%	46%
60–69	15%	13%	29%	30%
35–69	20%	13%	40%	44%
Women				
35–49	36%	22%	50%	39%
50–59	47%	25%	50%	45%
60–69	23%	12%	22%	18%
35–69	29%	19%	41%	37%

*Data from controls who participated fully in the risk factor survey.

TABLE 2: Passive smoking at home and risk of heart attack or coronary death (odds ratios and 95% confidence intervals [CI])

	Numbers of subjects		Crude odds ratio (CI)	Adjusted [†] odds ratio (CI)
	Cases	Controls*		
Men				
Non-smokers				
Exposed	22	34	1.04 (0.56–1.91)	0.97 (0.50–1.86)
Not exposed	161	259		
Ex-smokers				
Exposed	80	49	1.80 (1.20–2.74)	1.78 (1.13–2.79)
Not exposed	256	283		
Women				
Non-smokers				
Exposed	43	99	1.61 (1.04–2.47)	2.46 (1.47–4.13)
Not exposed	117	433		
Ex-smokers				
Exposed	23	30	1.63 (0.82–3.19)	1.48 (0.67–3.30)
Not exposed	57	121		

*Data from controls who participated fully in the risk factor survey.

[†]Adjusted for age and history of myocardial infarction or other ischaemic heart disease. Only subjects with information about history of heart disease are included in this table.

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TABLE 3: Passive smoking at work and risk of heart attack or coronary death (odds ratios and 95% confidence intervals [CI])

	Numbers of subjects		Crude odds ratio (CI)	Adjusted [†] odds ratio (CI)
	Cases	Controls*		
Men				
Non-smokers				
Exposed	27	79	0.90 (0.50, 1.60)	0.95 (0.51, 1.78)
Not exposed	48	126		
Ex-smokers				
Exposed	44	85	0.94 (0.56, 1.58)	0.88 (0.49, 1.59)
Not exposed	55	100		
Women				
Non-smokers				
Exposed	5	73	0.71 (0.19, 2.27)	0.66 (0.17, 2.62)
Not exposed	12	124		
Ex-smokers				
Exposed	5	20	1.45 (0.29, 7.18)	2.21 (0.33, 14.95)
Not exposed	5	29		

*Data from controls who participated fully in the risk factor survey.

†Adjusted for age and history of myocardial infarction or other ischaemic heart disease. Only subjects with information about history of heart disease are included in this table.

TABLE 4: Smoking behaviour and risk of heart attack or coronary death (odds ratios and 95% confidence intervals [CI])

	Numbers of subjects		Crude odds ratio	Adjusted [†] odds ratio (CI)
	Cases	Controls*		
Men				
Current smokers	324	259	2.26	2.71 (2.07, 3.53)
Ex-smokers	374	422	1.60	1.25 (0.98, 1.60)
Non-smokers	197	356	1.00	1.00
Total	895	1037		
Women				
Current smokers	127	168	2.95	4.70 (3.35, 6.58)
Ex-smokers	86	184	1.82	1.51 (1.06, 2.16)
Non-smokers	174	679	1.00	1.00
Total	387	1031		

Tests for linear trend in crude odds: Men: $\chi^2 = 45.3$, $df = 1$, $P < 0.001$; women: $\chi^2 = 60.1$, $df = 1$, $P < 0.001$.

*Data from controls who participated fully in the risk factor survey, completed the brief questionnaires or were interviewed at home.

†Adjusted for age (five year age groups) and history of myocardial infarction or other ischaemic heart disease. Only subjects with information about history of heart disease are included in this table.

ratios (4.70 for women and 2.71 for men) and ex-smokers and people exposed to passive smoking at home having lower, but still elevated, odds ratios compared with non-smokers.

Fibrinogen concentrations for participants in the risk factor survey (i.e., control subjects only) are shown in Figures 1 and 2. Women had consistently higher mean values than men. Mean fibrinogen concentrations were highest among current smokers, intermediate among ex-smokers and lowest for non-smokers. People exposed to passive smoking had higher levels than those not exposed (except for passive smoking at home for women). The differences were not statistically significant (due to high variability in the measurements) but were consistent with a dose-response relationship with cigarette smoke.

Discussion

The strength of this study is that it was

population-based with almost complete ascertainment of all cases of heart attack

or coronary death in the study population.²² Also the control group was obtained by random sampling from the same population. Before considering the magnitude of the effects shown, however, it is necessary to consider factors which might have affected their accuracy.

A potential source of bias in the case-control comparisons was that information on smoking was unobtainable for many case subjects who had died. Among fatal case subjects for whom this information was available, however, the patterns of smoking (current smoker, ex-smoker or non-smoker) and passive smoking were not different from those for non-fatal case subjects so it is plausible that fatal cases for whom information was unobtainable also had similar patterns of exposure. Further, Machlin et al. have suggested that smoking habits of people who have died are accurately reported by relatives and other informants.²³ Thus any bias caused by missing data for cases would probably be small.

Another source of bias is that people who respond to risk factor surveys are less likely than non-respondents to be smokers.²⁴ In our study non-respondents to the main survey (which included visiting a study centre and having physical measurements taken) were asked to reply to a brief mailed questionnaire, and some people who did not complete the brief questionnaire were visited at home and interviewed. For men aged 35–69 years, smoking prevalence rates were: 24% current smokers, 40% ex-smokers and 35% non-smokers for the main respondent group, compared with

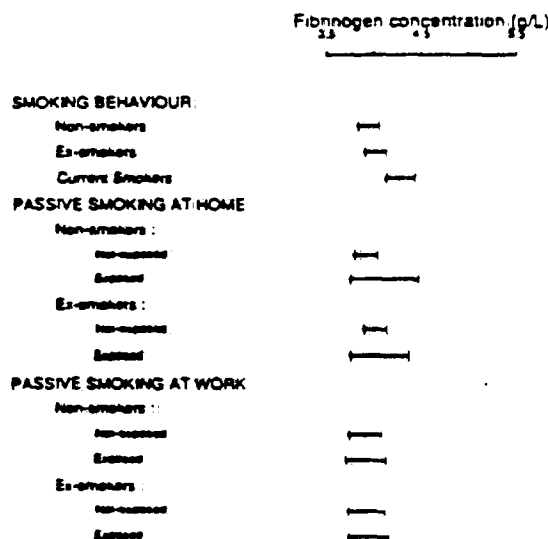


FIGURE 1: Fibrinogen concentrations among men in a community sample. (Mean concentration [g/L] for persons aged 50 years with body mass index ≥ 25 kg/m²). Confidence intervals based on standard errors from analysis of covariance of log transformed data.

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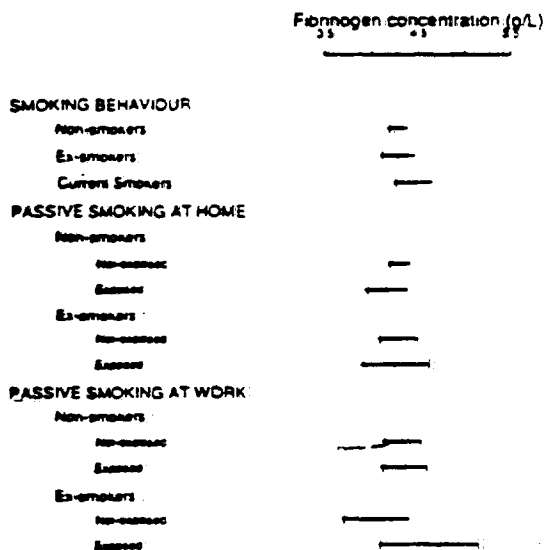


FIGURE 2. Fibrinogen concentrations among current, ex-smokers and non-smokers in a community sample. Mean concentration (g/L) for persons aged 50 years with body mass index of 25 (g/L); confidence intervals based on standard errors from analysis of covariance of log-transformed data.

28%, 42% and 30% for those who replied to the brief questionnaire and 29%, 42% and 29% for those interviewed at home. The corresponding rates for women were 14%, 19% and 67% for the main group, 21%, 13% and 66% for respondents to the brief questionnaire and 31%, 16% and 53% for those interviewed at home.

These results illustrate how non-response among control subjects can lead to underestimation of prevalence of smoking. It is reasonable to expect that if data had been obtained from everyone selected for the sample then the smoking rates and possibly prevalence of passive smoking among controls would have been higher and estimates of risk might have been somewhat lower.

As the control group was selected from the electoral roll, bias associated with this sampling frame should be considered. Although registration on the roll is compulsory for people born in Australia, about one in three of those aged 18–19 years are not enrolled and about one in 20 of those aged 20–30 years; beyond that age only about 1 in 50 eligible people are not enrolled.²² People born overseas are not necessarily required to enrol so they may be systematically under-represented by the roll.²³ The distribution of countries of birth in the risk factor survey was similar to that for the whole study population recorded at the 1986 Census: 86% of participants were Australian-born compared with 89% of the study population; 7% compared with 4% were born in the United Kingdom or Ireland; 4% compared with 2% were born in Northern Europe; 1% were born in

Southern Europe in both the survey and the 1986 Census and 1% were born in other countries.

Differences in the methods of data collection and truthfulness in reporting smoking habits might also have led to bias. Control subjects completed self-administered questionnaires whereas information for case subjects was obtained by a nurse-administered questionnaire or by mailed questionnaires completed by relatives of deceased case subjects. The most likely effect of these differences would be for case subjects to under-report their smoking and this would reduce the magnitude of estimates of risk.²⁴ It is also possible that case subjects might exaggerate the extent of their exposure to passive smoking, looking for "explanations" of their disease.

The effects of confounding factors need to be considered. For example, in this study previous myocardial infarction or history of ischaemic heart disease was found to be a significant confounder for smoking and the risk of myocardial infarction or coronary death. This is consistent with the observation that people with known heart disease are urged to give up smoking and often do so. Thus differences in magnitude of estimates of risk reported from various studies will be affected by differences in prevalence of heart disease and in the extent to which this is taken into consideration in the analysis.

Another potential confounder is socioeconomic status. Prevalence of cigarette smoking and hence the likelihood of exposure to passive smoking at home and possibly at work are higher among people

of lower socioeconomic status and so is the prevalence of heart disease in Australia.²⁵ For example, in this study the distributions of socioeconomic status as measured by education were significantly different among cases and controls, after adjustment for difference in age when control subjects were those who participated fully in the survey or completed the brief questionnaire (for men, $\chi^2 = 94.1$, $df = 4$, $P < 0.0001$; for women, $\chi^2 = 50.7$, $df = 4$, $P < 0.0001$). Adjustments for this confounder were not included in the analyses because of the very small numbers in most cross-classified categories. The effect of this factor would be to increase risks attributable to active and passive smoking by including effects of other socioeconomic variables.

Lack of statistical power is a limitation of this study. For many comparisons the numbers of subjects were small — most notably for exposure to environmental tobacco smoke at work, because few of the cases, especially among women, worked outside the home. Also, many factors increase the variation of fibrinogen measurements.²⁶ Although consistent differences were apparent, the results were not statistically significant and adding other covariates such as cholesterol levels did not reduce the variability. Far more subjects would have been needed to give unequivocal results.

On balance, the effects of bias and confounding could have led to overestimation of risks due to passive and active smoking. Nevertheless, the magnitude of increased risks which we found for passive smoking at home and for current smokers and ex-smokers are similar to those reported by others.^{1,2,27} In most studies of passive smoking and risk of heart disease, the exposure has been at home, from a smoking spouse. Dose levels from exposure at work have been reported to be higher because of the larger number of smokers and greater density of smoke.²⁸ Thus risk associated with exposure at work might be expected to be higher than with exposure at home. Our results do not support this as the odds ratios for exposure at work are less than one (except for women ex-smokers), although the confidence intervals are wide due to the small numbers of subjects. Alternative explanations should therefore be considered, such as: the possibility that dose levels of components of environmental tobacco smoke which cause heart disease are higher for those exposed at home than at work; or inaccurate reporting in this study

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of exposure at work (though fibrinogen levels are consistent with reported exposure); or effects of confounding variables not considered in this study.

The increased fibrinogen concentrations among current smokers and ex-smokers are as expected.¹⁰⁻¹² Increased fibrinogen associated with passive smoking has not to our knowledge been reported before. This finding, although not statistically significant (possibly because of the inadequate statistical power of the study), suggests that passive smoking increases the risk of heart attack or coronary death by at least some of the same mechanisms as active smoking. For fibrinogen, the effect is believed to be due to thrombogenesis rather than promotion of atherosclerosis.¹⁰

In summary, this study provides estimates of the prevalence of passive smoking in Australia in 1988-1989 and confirms previous findings of elevated risk of heart attack or coronary death associated with passive smoking at home. It also suggests that passive smoking is associated with increased concentrations of fibrinogen and so that at least part of its effect is thrombogenic.

Acknowledgements

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Australian patterns of tobacco smoking in 1989

(for editorial comment, see page 788)

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Objective: To estimate the national prevalence of smoking.

Design: A total of 4820 adults aged 16 years and over (2384 men, 2456 women) were surveyed throughout Australia in 1989 by a large market research company.

Setting: Interviews were conducted in the participants' homes.

Results: Overall, 30.2% of men and 27.0%

of women were current smokers; 28.8% of men and 18.3% of women were past smokers. The mean daily consumption of factory-made cigarettes among male smokers was 22 and among female smokers 18.9. Taking into account the published tar content of the brand smoked, it was estimated that the average daily exposure to tobacco tar for men was 204 mg and for women 157 mg.

Occupational and educational status were inversely related to the prevalence of smoking. The most popular packet size was 25 (preferred by 48% of smokers) and those in lower occupational and educational categories were more likely to purchase cigarettes in large packet sizes.

Conclusions: Comparison with an earlier series of studies commenced in 1974 showed that the national prevalence of smoking among adults has continued to fall, particularly among men.

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Garland, C., Barrett-Connor, E., Suarez, L., Criqui, M.H. and Wingard, D.L., "Effects of Passive Smoking on Ischemic Heart Disease Mortality of Nonsmokers: A Prospective Study," American Journal of Epidemiology 121(5): 645-650, 1985.

In this study, a community of older adults in suburban San Diego, California, was surveyed between 1971 and 1974 for the prevalence of heart disease risk factors. They were then followed for an average of 10 years to determine vital status and cause of death. The nonsmoking women were classified according to their husbands' smoking. Of the 695 nonsmoking women, 19 deaths from ischemic heart disease were recorded. It was reported that, compared to women married to husbands who had never smoked, women married to current or former smokers had a relative risk of 14.9. This was after statistically adjusting for age, systolic blood pressure, total cholesterol, obesity, and years of marriage. In a subsequent "erratum" the authors stated that the 14.9 value was an error and reported a corrected value of 2.7. (Am. J. Epidemiol.: 122, 1112, 1985.)

Criticisms

1. Neither the relative risk of 14.9 claimed in the original article, nor the "corrected" value of 2.7, was reported to be statistically significant.

2. The sample size was very small, consisting of only 19 deaths from heart disease.

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3. Questions have been raised in the literature, including by the 1986 National Academy of Sciences report, about the possible misclassification or misuse of the statistical test applied to the study.

4. The relative risk from ETS exposure was assessed by grouping nonsmoking women married to either current or to former cigarette smokers. Grouping current with former cigarette smokers provides a particularly weak estimate of ETS exposure.

5. Interpretation of the data is complicated due to 15 of the 19 deaths occurring in nonsmoking women married to husbands who had stopped at the time of entry into the study.

6. No information on any changes in smoking habits was available for the 10-year follow-up.

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EFFECTS OF PASSIVE SMOKING ON ISCHEMIC HEART DISEASE MORTALITY OF NONSMOKERS

A PROSPECTIVE STUDY¹

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The mortality attributable to ischemic heart disease as a result of cigarette smoking is greater than that due to lung cancer. Between 1972 and 1974, in a prospective study of a community of older adults in southern California, the authors tested the hypothesis that nonsmoking women exposed to their husband's cigarette smoke would have an elevated risk of fatal ischemic heart disease. Married women aged 50-79 years who had never smoked cigarettes ($n = 695$) were classified according to the husband's self-reported smoking status at entry into the study: never, former, or current smoker. After 10 years, nonsmoking wives of current or former cigarette smokers had a higher total ($p \leq 0.05$) and age-adjusted ($p \leq 0.10$) death rate from ischemic heart disease than women whose husbands never smoked. After adjustment for differences in risk factors for heart disease, the relative risk for death from ischemic heart disease in nonsmoking women married to current or former cigarette smokers was 14.9 ($p \leq 0.10$). These data are compatible with the hypothesis that passive cigarette smoking carries an excess risk of fatal ischemic heart disease.

ischemic heart disease; longitudinal studies; mortality; smoking, passive

Although cigarette smoke contains hydrocarbons, nicotine, carbon monoxide, and multiple carcinogens (1-4), interferes with pulmonary function (5, 6) and with cardiac function in persons with cardiovascular disease (7), and is a well established risk factor for emphysema (8), lung cancer

(9), and cardiovascular disease (10) in smokers, the health effects of passive smoking are a subject of much controversy (1, 11-15).

Nonsmokers in enclosed places with smokers are regularly exposed to smoke (15-17), the concentration of noxious agents in the air exceeds that in inhaled smoke (1), and a significant amount of nicotine is absorbed by exposed nonsmokers (18, 19). Recent studies suggest poorer pulmonary function in nonsmokers exposed to cigarette smoke at work (5), nonsmoking spouses exposed to smoking mates (6), and children exposed to smoking mothers (20-22), and an elevated frequency of respiratory tract symptoms in exposed children (21, 23-25). Epidemiologic studies in

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Greece (26, 27), the United States (28), Germany (29), Hong Kong (30), and Japan (31-34) indicated an excess risk of lung cancer in involuntary smokers. A prospective study by Garfinkel of the American Cancer society cohort in the United States (13) found no excess risk of lung cancer from involuntary smoking, although the negative findings may be due, at least partly, to misclassification of exposure to passive smoking (35).

A cancer-registry-based study in Lancaster County, Pennsylvania, revealed no cases of lung cancer in nonsmoking Amish persons (who are unexposed to passive smoking because they live in a closed society which forbids cigarette use) in a population of 12,000 observed for a seven-year period (36).

We hypothesized that an excess in ischemic heart disease might be shown in passive smokers, even when the amount of lung cancer induced would be too low to detect an excess risk, since mortality attributable to ischemic heart disease as a result of cigarette smoking is greater than that due to lung cancer (37). This is because lung cancer, even in heavy smokers, is less common than ischemic heart disease. We further hypothesized that nonsmoking women old enough to have died of coronary heart disease would have had spouses who provided the major source of cigarette smoke, because until recently most women had little exposure to cigarettes in the workplace.

We report here a prospective study of mortality from ischemic heart disease, as well as lung cancer, bronchopulmonary disease (chronic bronchitis, emphysema, and asthma), and all-cause mortality, in nonsmoking married women from a community of older adults who have been followed for 10 years.

SUBJECTS AND METHODS

Between 1972 and 1974, the entire adult community of Rancho Bernardo, California, a predominantly white, upper-middle-

class suburb of San Diego, California, was invited to participate in a survey for the prevalence of heart disease risk factors. Eighty-two per cent of adults in the population responded to the survey. Respondents were representative of the total population with regard to age and sex (38).

All participants had a standardized interview including questions about age; cigarette smoking; history of past hospitalizations for heart attack, heart failure, or stroke; and duration of marriage. Cigarette smoking was assessed as current, former, or never. The number of cigarettes smoked per day was determined only for current smokers, and no data were obtained about duration of smoking. Weight and height were measured in light clothing without shoes, and obesity was defined by body mass index ($\text{weight/height}^2 \times 100$). Before the interview, after the participant had been seated for at least five minutes, blood pressure was measured with a standard mercury sphygmomanometer. Plasma cholesterol was measured by an Autoanalyzer in a standardized Lipid Research Clinic Laboratory.

Vital status was determined by an annual mailing for an average of 10 years with an overall ascertainment rate of 99.6 per cent. Death certificates, obtained for all decedents, were coded by a certified nosologist according to the Eighth Revision of the *International Classification of Diseases, Adapted* (ICDA) (39). Deaths were categorized as ischemic heart disease (ICDA 410.0-414.9); cancer of the trachea, bronchus, and lung (ICDA 162-163); chronic bronchitis, emphysema, asthma, chronic obstructive pulmonary disease (ICDA 491-493); and all causes. A death certificate diagnosis of ischemic heart disease was validated by interviews with next of kin, physicians, and/or hospital records in 85 per cent of a subsample of this cohort. Procedures used at the time of the survey and follow-up have been described elsewhere (40-42).

After exclusion of women who had a prior

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history of heart disease or stroke or who reported that they currently or formerly smoked cigarettes, there were 695 currently married nonsmoking women who were divided into three mutually exclusive groups based on their husband's self-reported smoking status at the time of entry into the study: never, former, or current smokers. Length of follow-up was virtually identical in all groups. Differences in age-specific and total mortality rates were tested for significance by Fisher's exact test (43). Mortality rates were then age-adjusted by 10-year intervals, by the direct method and with the total study population as the standard. The Mantel-Haenszel test was used to compare age-adjusted rates (44). Cox's proportional hazards model (45) was used to adjust cumulative mortality rates and relative mortality risks for age, systolic blood pressure, plasma cholesterol, obesity index, and duration of marriage to current spouse. Regression coefficients were estimated by the method of maximum likelihood using a BMDP program (BMDP-2L) (46). Since we were testing previous findings concerning the risk of passive smoking, statistical significance was assessed at one-sided p levels of ≤ 0.05 and ≤ 0.10 .

Since probability values from the Cox model are based on asymptotic normality assumptions, the values must be interpreted with caution when cell frequencies are as small as those in the present study. The Cox regression was performed as a means of summarizing the results and controlling for simultaneous variation in possibly confounding risk factors.

RESULTS

Characteristics of the 695 currently married women aged 50-79 years who reported that they never smoked cigarettes were analyzed according to husband's smoking status at the initial examination (table 1). Women whose husbands never smoked or were former smokers were on the average older than wives of current smokers ($p \leq 0.05$). Wives of never smokers had been

married longer than wives of current smokers ($p \leq 0.05$). Although other differences were not significant, wives of nonsmokers tended to have higher systolic blood pressure and were slightly heavier for height. Plasma cholesterol did not vary significantly according to husband's smoking history.

Among nonsmoking women, those married to former or current smokers had the highest age-adjusted death rates from ischemic heart disease (table 2). Nearly one third of the age-adjusted mortality in women married to former smokers was attributable to ischemic heart disease. There were no deaths from bronchitis, emphysema, asthma, chronic obstructive pulmonary disease, or lung cancer in women married to never smokers, but there was one death from lung cancer in the wife of a former smoker and one death from chronic obstructive pulmonary disease in the wife of a current smoker.

Age-adjusted all-cause death rates were higher in wives of current smokers of 21+ cigarettes per day compared with those of smokers of 1-20 cigarettes per day (table 3), but this result was not statistically significant.

After adjustment for age, systolic blood pressure, total plasma cholesterol, obesity index, and years of marriage, the relative risk for death from ischemic heart disease for women married to current or former smokers at entry compared with women married to never smokers was 14.9 ($p \leq 0.10$). The regression results showed that systolic blood pressure, which was on the average 3.8 mmHg higher in wives of nonsmokers, significantly ($p \leq 0.05$) increased the risk of fatal ischemic heart disease. Women married to former smokers were not at excess risk of mortality from all causes (table 2).

Because of reports in the literature of increased mortality during widowhood (47-50), we examined whether bereavement might have explained the excess mortality in wives of current smokers. We reanalyzed

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TABLE 1
 Characteristics of nonsmoking women according to husband's cigarette smoking status at entry, 1972-1974

Wife's characteristics	Husband's smoking status		
	Never (n = 203)	Former (n = 395)	Current (n = 97)
	Mean \pm standard deviation	Mean \pm standard deviation	Mean \pm standard deviation
Age	64.6* \pm 6.7	65.4* \pm 6.9	62.1 \pm 7.4
Years of marriage	36.0* \pm 12.5	34.7 \pm 13.6	32.4 \pm 12.4
Systolic blood pressure	140.1 \pm 22.2	138.7 \pm 23.1	136.3 \pm 20.1
Obesity index	3.50 \pm 0.58	3.43 \pm 0.49	3.41 \pm 0.45
Plasma cholesterol	225.7 \pm 36.1	226.2 \pm 41.0	228.7 \pm 34.6

* Significantly greater than for wives of current smokers at $p \leq 0.05$.

TABLE 2
 Age-specific and age-adjusted 10-year mortality rates, 1974-1983, in nonsmoking women according to husband's cigarette smoking status at entry, 1972-1974

Age group of wives (years)	Husband's smoking status								
	Never			Former			Current		
	No. of deaths	Population at risk	%	No. of deaths	Population at risk	%	No. of deaths	Population at risk	%
Ischemic heart disease									
50-59	0	41	0.0	0	82	0.0	0	34	0.0
60-69	0	116	0.0	6	192	3.1	1	46	2.2
70-79	2	46	4.3	9	121	7.4	1	17	5.9
Crude rate	2	203	1.0*	15	395	3.8	2	97	2.1
Age-adjusted rate			1.2†			3.6			2.7
All causes									
50-59	1	41	2.4	3	82	3.7	3	34	8.8
60-69	12	116	10.3	21	192	10.9	6	46	13.0
70-79	9	46	19.6	21	121	17.4	3	17	17.6
Crude rate	22	203	10.8	45	395	11.4	12	97	12.4
Age-adjusted rate			11.0			11.0			13.3

* Lower ($p \leq 0.05$) than combined rate for wives of current and former smokers.

† Lower ($p \leq 0.10$) than combined rate for wives of current and former smokers.

the data excluding all deaths ($n = 29$) which occurred at any time after that of the husband and observed no change in the relative mortality risks from ischemic heart disease or from all causes (not shown). There was therefore no evidence that bereavement following the death of a spouse caused the excess mortality.

DISCUSSION

In this population of nonsmoking women aged 50-79 years, those married to current or former cigarette smokers had an elevated

risk of death from ischemic heart disease compared with wives of never smokers. Furthermore, the only two deaths attributable to lung cancer, bronchitis, emphysema, asthma, or chronic obstructive pulmonary disease in nonsmoking women were in women married to current or former smokers.

Although we followed 695 women for 10 years and observed an adjusted relative risk of 14.9 for ischemic heart disease in nonsmoking wives of current or former smokers, the total number of deaths was rela-

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TABLE 3

Ten-year all-cause mortality rates in nonsmoking women married to current smokers, according to number of cigarettes per day smoked by husband

No. of cigarettes per day smoked by husband	No. of deaths	Population at risk	Crude death rate (%)	Age-adjusted* death rate (%)
1-20	9	72	12.5	12.6
21+	3	25	12.0	21.1

* Adjusted for age by the direct method with the total population at risk as the standard.

tively small, and the results must be considered provocative rather than definitive. Nevertheless, we conclude that the association is real for the following reasons. First, it appears from the data (table 3) that a dose-response relationship exists between quantity of cigarettes smoked by the husband and the age-adjusted mortality rate of the wife. Second, the association of ischemic heart disease death with smoking by the spouse seems biologically plausible since carboxyhemoglobin concentration doubles in the blood of nonsmokers exposed to smokers in a poorly ventilated room for two hours (51), moderately elevated room levels of carbon monoxide can precipitate attacks of angina pectoris in persons with preexisting disease (7), and elevation of carbon monoxide and carboxyhemoglobin have been shown to decrease cardiac contractility and to raise left ventricular end-diastolic pressure in persons with cardiovascular disease (8).

Other explanations are possible (e.g., different smoking patterns in men with chronically ill wives) but seem unlikely, in that we excluded from the analysis all women with a history of cardiovascular disease. Widowhood, more common in the wives of smokers, could have resulted in increased risk of death for these women because of the so-called "broken heart" syndrome (47-50); however, bereavement was unrelated to the excess mortality in this cohort. Alternatively, cigarette smoking by a husband could reflect an otherwise less healthy lifestyle shared by the wife; this possibility was

not supported by comparisons of obesity, plasma cholesterol, and systolic blood pressure, all of which were similar or lower in wives of current smokers compared with other women. We should also note that the results of this study are confined to passive smoking exposures in the marriage in effect at the time of entry into the study, and exposures during previous (or subsequent) marriages would be missed. This would tend to have a generally conservative effect on the results.

To our knowledge, this is the first report of an increase in mortality from ischemic heart disease due to involuntary smoking. We hope that others will examine their data to determine whether this effect is present in other populations. If this association is confirmed, a strong public health argument exists for prohibition of smoking in enclosed spaces. Legislation is presently under consideration or in effect in many states and localities to this end (5).

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ERRATUM

The *Journal* has been notified by Dr. Cedric Garland of an error that went undetected by his co-authors and himself in a recent article (Garland et al., "Effects of Passive Smoking on Ischemic Heart Disease Mortality of Nonsmokers: A Prospective Study", *Am J Epidemiol* 1985;121:645-50). The authors incorrectly reported a multiple-adjusted (Cox) relative risk of ischemic heart disease in nonsmoking women married to men who ever-smoked of 14.9, with a p value of $p \leq 0.10$. The relative risk should be 2.7, with the p value remaining at $p \leq 0.10$ as originally reported. The correction does not affect the conclusions, and other values in the tables and elsewhere in the text are correct.

Amer. J. Epid.
V. 122 1985

SOCIAL FACTORS INFLUENCING DISEASE INCIDENCE

Berkman (1) states, "... pathways linking socio-environmental conditions and social support to physical health outcomes need to be more thoughtfully explored." This statement is particularly applicable to Native Americans on reservations where attitudes of the population toward the health care systems on the reservation have a profound impact on the ability of the physicians and other health care providers to deliver a quality of medical care commensurate with their degree of expertise.

More specifically, as a pediatrician who spent two years on a reservation, I was impressed by the widely known high incidence of acute and recurrent otitis media among the Native American children (2) and the too often associated hearing deficits with subsequent learning disabilities (3). Too often noted was a lack of parental compliance with prescribed medical regimens and routine follow-up care recommendations for acute and recurrent otitis media. I believe a cause and effect relation exists between the degree of parental noncompliance with prescribed medical regimens/routine follow-up care recommendations and an increased incidence of recurrent otitis media which, in turn, is known to be related to subsequent learning disabilities secondary to significant, recurrent, chronic hearing deficits. If better parental compliance could be achieved, the deleterious sequelae of recurrent otitis media, it is hoped, could be significantly reduced. I feel that the attitudes of any population toward a given health care system play a significant role in determining the ability of highly competent health care providers within a health care system to achieve

a noteworthy frequency of parental and patient compliance. Positive attitudes of a population toward a given health care system would probably result in increased patient and parental compliance which, in turn, would help decrease the frequency and severity of treatable pathologies.

In conclusion, the more one understands how social factors impact on disease incidence, the greater the likelihood that health care providers will be able to have a more positive impact on a given population and thus, generate a higher degree of patient/parental compliance resulting in reduced morbidity and mortality.

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Editor's note: In accordance with Journal policy, Dr. Berkman was asked if she wished to respond to Dr. DiNicola's letter, but she chose not to do so.

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Am. J. Epidemiol. 125 8:541,
1987

RE: "EFFECTS OF PASSIVE SMOKING ON ISCHEMIC HEART DISEASE MORTALITY OF NONSMOKERS: A PROSPECTIVE STUDY"

Garland et al. (1) reported initially that as a result of a near 10-year prospective study, with data analyzed by highly sophisticated statistical methods allowing adjustment for various factors, it was found that wives of current or former smokers had an increased relative risk for death from ischemic heart disease of 14.9, highly suggestive if not nominally significant ($p \leq 0.10$). A subsequent erratum (2) states that the relative risk of 14.9 was erroneous and should have been 2.7, p remaining at ≤ 0.10 . Conclusions in the report were stated not to be affected, other values in the tables and elsewhere to be correct.

However it was the 14.9 relative risk which was at the heart of the initial report. No other relative risks were cited in the report. The 14.9 relative risk was repeated several times in the report and motivated the suggestion that legislation might be needed. A nonsignificant relative risk of only 2.7 hardly conveys the authority for such action. Furthermore, I note that the authors give some justification for using one-sided p levels on the basis that they were testing previous

findings. Yet in their final paragraph they state that to their knowledge, their report was the first to relate increased mortality from ischemic heart disease to involuntary smoking. In that case, p should be ≤ 0.20 , not significant at all, and even less supportive of the need for action.

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THE FIRST AUTHOR REPLIES

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The error to which Mantel refers (1) was corrected previously (2). The results of the study (3) remain the same overall: nonsmoking women married to men who smoked had higher total ($p \leq 0.05$), age-adjusted ($p \leq 0.10$), and multiple-adjusted ($p < 0.10$) rates of fatal ischemic heart disease than those married to men who did not. The findings have been replicated in women by Hirayama (4) and Gillis et al. (5); and in MRFT men by Svendsen et al. (6).

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RE: "EXCESS MORTALITY FROM STOMACH CANCER, LUNG CANCER, AND
ASBESTOSIS AND/OR MESOTHELIOMA IN CROCIDOLITE MINING DISTRICTS IN
SOUTH AFRICA"

Permit us to draw your attention to the following aspects of an article published in the *American Journal of Epidemiology* on mortality in crocidolite mining districts in South Africa (1).

In the abstract it is stated, "These findings..... are likely to be due to exposure to South African crocidolite during mining and milling or to environmental contamination." In the case of white females and colored females, most personnel were subject to environmental exposures only, which is not evident from the authors' remarks on page 38.

While the authors stress that until 1977 asbestosis and/or mesothelioma were combined under ICD-8-467, not a single case of asbestosis is known to have been contracted by environmental exposure to asbestos.

The investigations were based entirely on death certificates. The accuracy of death certificates has been questioned all over the world. In South Africa there is a special problem in that in the rural areas of the Northern Cape—and elsewhere in this vast country—the bulk of death certificates of coloreds have not been completed by medical personnel but by members of the South African police. During the early years under review this may also have applied to isolated white farmers and their families. This practice appar-

ently still continues according to inquiries to the legal advisers of the South African Medical Association.

In the South African Mesothelioma Register, there was in October 1983 a total of 1,228 cases since 1956 of which 510 cases had no known connection with asbestos. Some of these may be spontaneous cases (2). By March 1985, the total had increased to 1,459 and the number of "unknown" and/or spontaneous cases to 639, i.e., more than 50 per cent of the increase (J. C. A. Davies, National Centre for Occupational Health, personal communication).

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2. National Centre for Occupational Health, annual report for 1983.

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THE AUTHORS REPLY

Mr. Hart's statement that "In the case of white females and colored females, most personnel were subject to environmental exposures only" (1) strengthens our deduction that "a major part of the impact may have been through environmental rather than occupational exposure" (2, p. 38). Our deduction

was based on the increased risk for asbestosis and/or mesothelioma deaths that occurred "not only for males but also for females, who, according to records, had not been employed on mines until 1950 and then at lower rates than males in most districts" (2, p. 38).

Mr. Hart does not cite a reference for his statement

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He, Y., et al., "Women's Passive Smoking and Coronary Heart Disease," Chung Hua Yu Fang I Hsueh Tsa Chih 23(1): 19-22, 1989.

This was published as a Chinese article with an English language abstract. It reports a case-control study of 34 coronary heart disease cases among women, who were classified according to their own and their husband's smoking behavior. The cases were otherwise matched to controls on the basis of age, race, residence and occupation. The authors report a statistically significant increase in the heart disease odds ratio for nonsmoking women married to smokers. A significant dose-response relationship was also claimed.

Criticisms

1. The English language abstract provides very few details on which to evaluate the article.

2. There are several editorial and bibliographical errors which are apparent even though only the abstract is available in English. These may raise questions about the overall credibility of the report.

3. The report is based on a small sample size of only 34 heart disease cases.

4. The report comes from a Chinese military hospital, a data source of unknown reliability.

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5. This is a case-control study, and suffers from common problems with such studies, such as difficulties in establishing appropriate control groups and controlling for potential confounding variables.

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女性被动吸烟与冠心病

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摘要 对34名女性冠心病者(冠状造影确诊者22例、心肌梗塞者12例)进行了被动吸烟与冠心病关系的病例对照研究。发现女性被动吸烟者患冠心病的比数比(OR)为3.0~3.5($P < 0.05$)；被动吸烟年限及累积吸入量与其患冠心病的OR间有明显的剂量反应关系；多元Logistic回归分析表明在诸多冠心病危险因素中，被动吸烟对女性危害较大。同时发现被动吸烟者的血清LDL-C、HDL-C、apoA1及apoB水平异常。

关键词 冠心病 冠状造影术 被动吸烟

已有实验研究表明：香烟燃烧产生的副烟流含有与吸烟者吸入的主烟流相似的有害物质，并以类似的方式危害吸入副烟流的不吸烟者，即被动吸烟者^[1,2]。一些文献报告：被动吸烟与肺功能损害、肺癌、冠心病的发生及心绞痛的诱发等有关^[3-6]。国内这方面的研究较少，并偏重对肺功能影响的研究^[7]。本文报告了在女性住院病人中调查被动吸烟与冠心病关系的结果。

材料与方法

采用1:2配对的病例对照方法。病例为1985~1987年间在我校西京医院经冠状造影确诊的冠心病患者和部分心肌梗塞患者。对照包括：入院初可疑冠心病、后经冠状造影证实的冠脉正常者；经冠心病诊断标准(1980年全国内科学学术会议制订)排除冠心病的心肾、内分泌及某些外科疾患的住院者；按国际上推荐方法^[8]所设的，在普查人群中随机抽样的非冠心病者。分成住院和人群两个对照组并全部经心电图运动试验检查(其中5例加做心得安试验，排除假阳性)。

按统一的调查表及方式由1人逐例询问调查。其内容包括：人口统计特征、本人及其丈夫既往的吸烟情况、涉及开始吸烟年龄、平均每日吸烟量、何时戒烟等问题。吸烟和被动吸烟的定义为：①每天吸烟1支以上，时间长于1年者为吸烟者。丈夫在调查时已停止吸烟5年以上者为戒烟者；②妻子不吸烟但与吸烟的丈夫共同生活长于5年者为被动吸烟者；③丈夫

婚前就吸烟，其妻子暴露于烟雾的时间以结婚时间为起点，而婚后才吸烟者以开始时间为起点，以离婚、丈夫戒烟或去世为止点；④单身妇女与丈夫不吸烟的妻子同视。病例及对照的合作程度较好，采用同期录音并对部分研究对象的丈夫再次调查，核对其准确性。

统计前，复查住院病历，剔除误诊病例、与吸烟有关的疾患者和各组中的主动吸烟者。共选出病例34例(冠状造影确诊者22例、心梗患者12例)、医院对照34例(含冠状造影者13例)、人群对照34例，按民族、职业、居住地相同、年龄相差 ± 5 岁1:2配对。采用1:2配对统计法^[9]、分层及多元Logistic回归模型分析法处理上述资料，多元分析由Sun-68000型计算机完成。

结 果

一、病例组与对照组的可比性检验

两组在年龄、文化程度、结婚年限等方面经均衡性检验差异均无显著性。平均年龄病例组 53.70 ± 4.28 岁、对照组 52.93 ± 5.24 岁($t = 1.282, P > 0.05$)。

二、被动吸烟

表1为1:2配对比较结果，其OR值为3.00。成组比较结果为3.519。两组结果接近，其95%可信限均大于1。即丈夫吸烟的妻子患冠心病的危险性是丈夫不吸烟妻子的3倍以上。

1. 剂量反应关系：丈夫每日平均吸烟量、妻子被动吸入年限及累积吸入量(—丈夫平均

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表 1 病例和对照的被动吸烟情况

		对 照		
		+	+	-
病	+	4	12	9
例	-	3	4	2
OR		3.00		
OR 95% CI		1.256~7.168		
$\chi^2(P)$		6.117 (<0.05)		

日吸烟量×妻子吸入年限)与患冠心病的OR值之间可见显著的剂量反应关系(表2),即随被动吸入量及年限的升高,患冠心病的危险性愈大。

表 2 被动吸入量及年限与冠心病的关系

	病例	对照	OR	χ^2
丈夫日吸烟量(支/日)				
0	9	38	1.000	---
<20	12	22	2.303	1.880
>20	13	8	6.861	10.098**
被动吸入年限(年)				
0	9	38	1.000	---
<10	4	9	1.877	0.266
<20	8	11	3.071	2.581
>20	13	10	5.489	8.230**
累积吸入量(支·年)				
0	9	38	1.000	---
1~199	4	11	1.535	0.066
200~399	6	11	2.303	1.009
400~599	6	5	5.067	4.054*
600*	9	3	12.667	11.358**

* $P<0.05$ ** $P<0.01$

2. 与临床分型的关系: 病例组按临床诊断分为心绞痛型21例, 心梗型13例。被动吸烟情况在两型间的分布基本一致($\chi^2=1.298$, $P>0.5$)。病例与对照间的比较见表3。结果示: 心绞痛型与被动吸烟有显著联系; 心梗型的OR值虽大于1, 但未达到显著性水平, 可能与样本小有关。

3. 被动吸烟者血脂及载脂蛋白水平观察: 在控制了年龄、体重指数等混杂因素并经分层

表 3 被动吸烟与临床分型的关系

	心绞痛型		心肌梗塞型	
	吸	不吸	吸	不吸
病例	17	4	8	5
对照	20	22	10	16
OR	4.675		2.550	
χ^2	5.035		1.018	
P	<0.05		>0.05	

比较后发现: 被动吸烟者血清HDL-C及apoAⅠ水平下降, 而LDL-C、apoB及apoB/AⅠ水平较非被动吸烟者的水平高, 其中对照组的HDL-C、apoAⅠ和apoB/AⅠ的水平在两者间相差显著, 见表4。

三、多元 Logistic 回归模型分析

为排除和分析其他危险因素在冠心病发病中的影响, 估计调整后各因素的相对危险度, 本研究引入多元 Logistic 回归模型, 对与冠心病发病有关的7个危险因素进行了统计处理。其中包括: 既往高血压病史 x_1 , 高血压家族史 x_2 , 冠心病家族史 x_3 , 被动吸烟史 x_4 , 饮酒史 x_5 , 体育锻炼情况 x_6 , 既往高血脂病史 x_7 , 结果见表5。

讨 论

本研究采用医院和人群两种对照的意义, 在于避免或减少因冠脉造影适应证及其他因素带来的人院选择偏性和暴露偏性^[8]。经设计和统计检验表明, 两对照组基本同质, 与病例组的可比性较好。

对女性被动吸烟的规定比主动吸烟困难得多, 而且受烟雾浓度、室内通风、周围环境的影响, 虽已有多项尝试, 但至今还没有一种大家公认的标准^[11]。以丈夫吸烟的情况来估计女性被动吸入量是目前常用的方法之一^[12, 14, 16]。其优点是简单、易行、相对客观。

女性被动吸烟者患冠心病的OR为3.0~3.5, 95%可信限大于1, 其吸入量与OR值有显著的剂量效应关系; 被动吸烟与心绞痛有关, 这些与国外的一些报告相同, 在控制了其他因素混杂的情况下, 此关系依然存在, 这说

表 4 女性被动吸烟者血脂及载脂蛋白水平观察 ($\bar{x} \pm s$)

分 组	被 动 吸烟史	例 数	TC (mmol/L)	LDL (mmol/L)	HDL (mmol/L)	LDL/HDL	apoA1 (g/L)	apoB(g/L)	apoB/apoA1
对 照 组	-	26	4.42 \pm 0.65	2.34 \pm 0.68	1.41 \pm 0.18	1.74 \pm 0.51	1.27 \pm 0.24	0.71 \pm 0.17	0.61 \pm 0.19
	+	20	4.47 \pm 0.68	2.52 \pm 0.68	1.29 \pm 0.18*	1.98 \pm 0.60	1.11 \pm 0.23*	0.74 \pm 0.14	0.67 \pm 0.22
冠心病组	-	9	5.15 \pm 0.86	3.35 \pm 0.86	1.26 \pm 0.21	2.75 \pm 0.79	0.95 \pm 0.18	1.03 \pm 0.17	1.21 \pm 0.40
	+	24	5.80 \pm 0.73*	3.85 \pm 0.71	1.12 \pm 0.17*	3.42 \pm 0.74*	0.81 \pm 0.13*	1.16 \pm 0.20	1.36 \pm 0.22*

* $P < 0.05$ P 值系指被动吸烟者与非被动吸烟者比较

表 5 冠心病危险因素的条件 Logistic 回归分析结果

入选变量	B_i	$Var(B_i)$	$S_2(B_i)$	$STD(B_i)$	OR	G^*	P
被动吸烟史 x_1	0.406	0.069	0.083	4.871	1.500 4	16.93	< 0.01
既往高血压史 x_2	0.714	0.052	0.227	3.147	2.042 8	8.90	< 0.01

* G 为统计量,服从 χ^2 分布

明被动吸烟与本研究组中女性冠心病的统计学联系是成立的。另外,本研究对被动吸烟者血脂及载脂蛋白水平观察的结果提示:女性被动吸烟者发生冠心病,可能是通过某些脂代谢途径。对此生物学方面的研究还有如下进展:据 Scott 报告,室内 85% 的烟雾是来自副流烟雾,而副流烟雾比主流烟雾含有浓度更高的有毒气体成份,因而受其危害可能更大。实验表明:被动吸入时血中 COHb 水平明显升高,对有心肺疾病患者的影响更为明显^[1]。Aromow 对 10 名稳定性心绞痛患者的观察表明,暴露在通风不好的烟雾中,2 小时后血清 COHb 升高 1 倍,体力负荷诱发心绞痛的时间缩短 1/3^[2],机制有待探明。

在我国,15 岁以上人口总吸烟率为 33.88%,男性高达 61%^[10]。吸烟的间接公害尚未引起人们足够重视。尽管本研究的例数较少,其代表性局限,但仍提示:被动吸烟与冠心病有一定的关系。在大力宣传戒烟的同时,应立法在公共场所禁止吸烟。

Women's Passive Smoking and Coronary Heart Disease He Yao, et al., Department of Epidemiology Fourth Military Medical College of P.L.A. Xi'an

Thirty-four women CHD cases (22 cases diagnosed

by coronary arteriography and 12 myocardial infarction) and 68 of non-CHD controls (34 hospital based and 34 population based), matched on age (within five years), race, residence, occupation (and case is to control as 1:2), were interviewed regarding the smoking habits of themselves and their husbands. The odds ratio (i. e. OR) of non-smoking women's CHD associated with having a smoking husband are 3.00~3.52, OR 95% CI do not include 1. Significant dose-response relationship between OR of women's CHD and their husband's cigarette consumption, duration of passive smoking and cumulative quantity of passive smoking were found in the study. The logistic regression model analysis with other CHD risk factors showed that the relationship with CHD and passive smoking still existed. It was found that the metabolism of HDL-cholesterol and apolipoproteins with passive smokers was abnormal.

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甲醛脲分光光度法直接测定酒中锰

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甲醛脲作显色剂应用于锰的测定已有报道^[1,2]。本文在此基础上, 探讨了甲醛脲比色法直接测定各种蒸馏酒中的微量锰。

一、材料与方法

1. 仪器和试剂: 721型分光光度计; 10.0 $\mu\text{g}/\text{ml}$ 锰标准溶液; 甲醛脲溶液(8.0 g 盐酸羟胺加入 37% 甲醛 4 ml, 稀释至 200 ml); pH=10.0 氨性缓冲液; 10% 盐酸羟胺溶液; 0.10 mol/L EDTA 溶液。

2. 分析方法

(1) 标准曲线的制备: 取锰标准溶液 0、0.10、0.20、0.40、0.80、1.20、1.60 和 2.00 ml, 分别置 25 ml 比色管中, 加水至 20 ml, 加入 1.0 ml 甲醛脲溶液和 1.0 ml 缓冲溶液, 混匀, 放置 5 分钟; 加入 1.0 ml 盐酸羟胺溶液和 1.0 ml EDTA 溶液, 并用水稀释至 25 ml, 充分混匀, 于室温放置 10 分钟。在 450 nm 处, 用 3 cm 比色皿, 以试剂空白为参比测定吸光度。将所得吸光度绘制标准曲线。本法 20 ml 中锰含量在 1.0~20.0 μg 符合比耳定律。

(2) 样品分析: 分取蒸馏酒 20 ml 或适量(锰含量不大于 20 μg), 置 25 ml 比色管中, 然后按标准曲线的步骤测定样品吸光度。

二、结果与讨论

1. 精密度试验: 在不同时间内, 对 4 份不同锰含量的酒样, 按上述方法重复测定 7 次, 其测定标准差分别为 0.136、0.288、0.104、0.129, 变异系数在 1.57~6.10% 之间, 说明精密度是满意的。

2. 准确度试验: 取含不同浓度锰的酒样各 20.0 ml, 分别加入锰标准溶液, 按上述方法操作, 其回收率在 95.0~102.0%, 平均回收率在 98.5%。说明方法的回收率良好。

3. 干扰离子的影响: 测定结果表明, 在盐酸羟胺和 EDTA 的存在下, Cu^{2+} 、 Pb^{2+} 、 Zn^{2+} 、 Cd^{2+} 、 Cr^{3+} 、 Al^{3+} 、 As^{3+} 和 Ag^{+} 为 10 mg/L, Fe^{2+} 、 Fe^{3+} 和 Sn^{2+} 为

5 mg/L 对锰的测定均无干扰。酒精度从 10~70 度范围内对锰的测定亦无影响。因此, 本法选择性较好, 能直接测定蒸馏酒中锰。

4. 方法的比较: 取 4 份不同的酒样, 分别用本法 and 原子吸收法测定酒中锰含量, 两种方法测定结果差异无显著性($P < 0.05$, 附表)。

附表 二种方法测定结果的比较

方 法	酒 样 (mg/L)			
	1	2	3	4
本 法	0.195	0.260	0.085	0.340
原子吸收法	0.188	0.252	0.084	0.352

5. 显色反应的稳定性: 在 pH 为 10 的介质中, 锰与甲醛脲的显色反应在 5 分钟后能达到最大显色, 且吸光度至少能稳定 3 小时。但为了消除铁的干扰, 加入 EDTA 溶液后需在室温放置 10 分钟后进行比色。

三、小结

用甲醛脲分光光度法测定蒸馏酒中微量锰, 样品不需要进行消化处理就能直接测定, 操作简便, 灵敏度高, 精密度和准确度也较好; 本法与原子吸收法比较, 测定结果差异无显著性。本法不仅能直接测定蒸馏酒中的锰, 而且也适用于测定其他样品中锰的含量。

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2023511737

Passive Smoking in Females and Coronary Heart Disease

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ABSTRACT

Thirty four cases of women with coronary heart disease (CHD) (22 cases diagnosed by coronary arteriography and 12 cases diagnosed as having myocardial infarction) were used in an investigation designed to assess the association between passive smoking in women and the establishment of CHD. The odds ratio (OR) of non-smoking women developing CHD as a result of exposure to passive smoke is 3.0-3.5 ($p < 0.05$). A dose response relationship was detected between the number of passive smoke exposure years and the increase in OR for CHD. Multiple regression analysis shows that of the many risk factors for CHD, passive smoke exposure is significantly correlated with CHD. Women exposed to passive smoke also showed abnormal levels of serum LDL-C, HDL-C, apoA1 and apoB.

Key Words

Coronary heart disease, coronary arteriography, passive smoke

Experimental investigations have demonstrated that the chemical constituents generated in the sidestream smoke often contain the same harmful chemicals as in mainstream smoke inhaled by smokers, and that there is considerable adverse effects contributed by sidestream smoke to non-smokers who are passively exposed.^{1,2} A number of reports have appeared showing a correlation between passive smoke and the damage to lung functions, increased incidence of lung cancer, and angina pectoris.³⁻⁶ A limited number of investigations have been focused on the subject of passive smoke in the People's Republic of China, and have only concentrated on studying the influence of passive smoking on lung functions.⁷ In this communication we report the relationship between passive smoke exposure and female patients who were hospitalized because of coronary heart disease.

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Materials and Methods

Subjects consisted of patients hospitalized between 1985-1987 and diagnosed as having coronary heart disease and myocardial infarction. They were matched employing the 1:2 method as follows: those who were admitted because of possible coronary heart disease and were later confirmed by coronary arteriography to be normals; patients with endocrine dysfunctions but free of CHDs; and people randomly selected from the population. Thus three groups were included in the present investigation: Group 1, those hospitalized and diagnosed with CHDs or myocardial infarction; Group 2, those hospitalized with endocrine problems but having no symptoms of CHDs, and Group 3, normals from the general population.

Each of the subjects in the three groups was interviewed using a standardized questionnaire. Some of the questions addressed included: subjects and the spouses smoking history, the age at which smoking began, the average daily cigarette consumption. Active and passive smoking were defined as follows: 1. Smoking at least one cigarette per day for a period of at least one year. The spouse is defined as an ex-smoker if he has already stopped smoking at least 5 years at the time of interview. 2. Wife who is a non-smoker but has lived with a smoking husband for at least 5 years is classified as a passive smoker. 3. If husband is a smoker before marriage, the wife exposure begins at time of marriage. Alternatively, the wife can become exposed after marriage if the husband picks up the smoking habit after marriage. Total exposure time is determined by divorce, death of husband, or when the husband quits smoking and becomes an ex-smoker. 4. Single female is considered to be equivalent to a female without a smoking spouse. To verify the accuracy of the data collected by the structured interview, tape recording was used and randomized re-interview was performed.

Subject group consist of 34 cases (22 cases diagnosed with CHD, and 12 cases diagnosed with myocardial infarction). Control group consist of 34 hospitalized subjects (with 13 suspected of CHDs but later confirmed to be normals) and 34 randomly selected matched for race, occupation, residence and age (± 5 years). Multiple regression analysis was performed and the data analyzed using a Sun-68000 electronic calculator.⁹

Results

1. Comparison between the Subject and the Control Groups

No significant differences exist between the two groups in regard to age, education, the marriage age. The mean ages of the diseased and control groups are 53.7 ± 4.28 and 52.93 ± 5.24 , respectively ($t=1.282$, $p>0.05$)

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2. Effects of Passive Smoking

Table 1 shows a comparison between disease and paired control groups. The OR of getting CHD for nonsmoking women living with a smoking husband is 3.00, with a 95% CI of 1.256-7.168, i.e. the risk of women getting CHD is 3 times higher for those with husbands that smoke compared to those with nonsmokers husbands.

Table 1. A comparison of Passive Smoking Status in Diseased and Control Groups

		Control Group		
		+	+	-
		+	-	-
Diseased	+	4	12	9
Group	-	3	4	2
OR		3.00		
OR 95% CI		1.256-7.168		
X ² (P)		6.117 (< 0.05)		

A. Dose Response Relationship

Table 2 illustrates the association between husbands' average daily cigarette consumption, passive smoke exposure years, cumulative passive smoke amount index, and the ORs of getting CHD. There is a noticeable dose response relationship, i.e. as the amount of passive smoke exposure increases, the risk of getting CHD also becomes greater.

Table 2. Dose Response Relationship between Passive Smoke Exposure and CHDs

	Subject	Control	OR	X ²
Husbands daily cigarette consumption				
0	9	38	1.000

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<20	12	22	2.303	1.880
>20	13	8	6.861	10.098**
Passive Smoke Exposure Years				
0	9	38	1.000
≤10	4	9	1.877	0.266
≤20	8	11	3.071	2.581
>20	13	10	5.489	8.230**
Cumulative Passive Smoke index (Years)				
0	9	38	1.000
1-199	4	11	1.535	0.066
200-399	6	11	2.303	1.009
400-599	6	5	5.067	4.054*
600*	9	3	12.667	11.358***
<hr/>				
*P<0.05		**P<0.01		

B. Association with Clinical Diagnosis

In the patients group, 21 cases were diagnosed with angina pectoris and 13 cases with myocardial infarction. The number of passive smokers in both clinical settings is similar ($\chi^2 = 1.298$, $p > 0.5$). These results are illustrated in Table 3. The results show that angina pectoris is clearly and significantly correlated with passive smoking. Although myocardial infarction in the passive smoking group show an OR of greater than 1, it did not reach statistical significance, which may be related to the small sample size.

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Table 3. Clinical Diagnosis in Passive Smoke Group

	Exposure to Passive Smoke		Exposure to Passive Smoke	
	Yes	No	Yes	No
	Angina Pectoris		Myocardial Infarction	
Subject Group	17	4	8	5
Control Group	20	22	10	16
OR	4.675		2.550	
χ^2	5.035		1.018	
P	<0.05		>0.05	

C. Blood cholesterol and Lipoprotein Level Changes in Passive Smokers

By controlling for age, weight, and other risk factors, a decrease in serum HDL-C and apoA1 levels was found in passive smokers, whereas LDL-C, apoB and apo B/A1 levels are higher than those not exposed to passive smoke. The level of HDL-C, apoA1 and apoB/A1 levels are significantly different between the subject and control groups (Table 4)

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Table 4. Blood Cholesterol and Serum Lipoprotein Levels in Female Passive Smokers

	Control Group		CHD Group	
	Non-exposed	Exposed	Non-exposed	Exposed
Number	26	20	9	24
Total cholesterol (mmol/L)	4.42±0.65	4.47±0.68	5.15±0.86	5.80±0.73*
LDL (mmol/L)	2.34±0.68	2.52±0.68	3.35±0.86	3.85±0.71
HDL (mmol/L)	1.41±0.18	1.29±0.18*	1.26±0.21	1.12±0.17*
LDL/HDL	1.74±0.51	1.98±0.60	2.75±0.79	3.42±0.74*
apoA1 (g/L)	1.27±0.24	1.11±0.23*	0.95±0.18	0.81±0.13*
apoB (g/L)	0.71±0.17	0.74±0.14	1.03±0.17	1.16±0.20
apoB/apoA1	0.61±0.19	0.67±0.22	1.21±0.40	1.36±0.22*

*P<0.05, P values refer to comparison between non-exposed and exposed cases.

3. Multiple Logistic Regression Analysis

Seven risk factors believed to contribute to CHD were subjected to logistic regression analysis. These factors include: history of hypertension (x1), family history of hypertension (x2), family history of CHD (x3), history of passive smoke exposure (x4), history of drinking (x5), exercise performance test (x6) and history of hypercholesterolemia (x7). The results are shown in Table 5.

Table 5. Multiple Regression Analysis of CHD Risk Factors

	B1	Var(B1)	S(B1)	STD(B1)	OR	G	P
History of Passive smoke	0.406	0.069	0.083	4.87	1.5004	16.93	<0.01
History of Hypertension	0.714	0.052	0.227	3.147	2.0429	8.90	<0.01

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DISCUSSION

To avoid and minimize bias introduced in studies using hospitalized subjects, the present investigations compared the subjects groups to two control groups, one group consisting of patients hospitalized for reasons other than CHDs, and a second group randomly selected from the general population. These two control groups are compared to the CHD-diseased group.

Investigations on the effects of passive smoking in females are more difficult to perform than comparable studies aimed at the effects of active smoking, because the effects of passive smoking may be dependent on such factors as humidity, ventilation and other indoor environmental considerations. Studies to date have not been able to produce a widely accepted standardized protocol for this type of investigation. One of the methods which have been used to assess passive smoke exposure in females relies upon the smoking status of spouses, which have been used in several previous published reports.^{1,4,6} The method appears to provide a certain degree of simplicity, feasibility, and relative objectivity.

Female passive smokers have an OR of 3-3.5 in getting CHD, with 95% CI greater than 1. The exposure dose is associated with angina pectoris, in agreement with results of other investigators. The associations remain after adjusting for potential confounders, suggesting that there is a direct correlation between passive smoking and CHD in females. Additionally, our investigations also showed alterations in blood cholesterol and lipoprotein levels, indicating that an alteration in the metabolism of cholesterol and/or lipoprotein could contribute to CHD in female passive smokers. According to Scott et al.¹, 85% of indoor smoke is due to sidestream smoke, which is known to contain a higher concentration of many toxic chemicals than mainstream smoke, and presumably exhibit a more pronounced adverse health effect. Previous studies have shown that an increase in blood COHb levels capable of producing an obviously untoward effect in people with heart and lung diseases.¹ Arrownow studied 10 subjects with angina pectoris, and reported a doubling of blood COHb 2 hours after exposure to indoor tobacco smoke in a poorly ventilated environment. These subjects also showed a 33% reduction in time of exercise before reaching a perceived exertion. The mechanism, however, remains to be investigated.

In People's Republic of China, 33.88% of population age >15 years are smokers and 61% of males regular smokers. The indirect public health consequences of smoking has not received enough attention. Despite the limited number of cases used in the present investigation which obviously have severe restrictions, it suggests that passive smoking is related to CHD in females. Thus, smoking in public should be restricted

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Helsing, K.J., Sandler, D.P., Comstock, G.W. and Chee, E., "Heart Disease Mortality in Nonsmokers Living With Smokers," American Journal of Epidemiology 127(5): 915-922, 1988.

In 1963, a private census was taken in Washington County, Maryland, at which time information was collected on smoking habits and a variety of other variables. Death certificates were monitored for the subsequent 12-year period, ending in 1975. The study itself focused on white nonsmoking men and women aged 25 or over who were available during the follow-up period. ETS exposure was based on the presence and extent of smoking by other persons also living in the household. The endpoint data concerned deaths from "arteriosclerotic heart disease," which includes coronary heart disease.

Based on 1358 deaths from arteriosclerotic heart disease, Helsing, et al. reported statistically significant risk elevations in both sexes associated with household exposure, after adjusting for age, marital status, years of schooling, and quality of housing. For men, the relative risk was 1.31, but there was "little evidence of a dose-response relation." (p. 915) Among women, the relative risk was 1.24, and a statistically significant dose-response relationship was also reported.

Criticisms

1. Attempts to estimate ETS exposure from data on household smoking were particularly inadequate because the data

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were collected on smoking in 1963, yet many changes probably occurred in smoking behavior during the subsequent 12-year follow-up. This concern was noted by the authors.

All smoking data were obtained in the 1963 census, so no provision can be made for changes in smoking habits which we know took place as a result of publicity about health effects of smoking. (p. 921)

2. Other changes in the compositions of the households may have occurred during the follow-up period. Although the authors assume that any changes might influence the ETS comparison groups randomly, this is mere speculation.

We also have no data on changes in the household composition which may have occurred prior to or after 1963. Thus, we implicitly assume that any such changes occurred randomly in the population. (p. 921)

3. Although an attempt was made to adjust statistically for some potential heart disease risk factors (age, sex, etc.), no data were available on many potentially important risk factors for heart disease such as diet, exercise, blood pressure, and cholesterol.

We have very little data on other risk factors for arteriosclerotic heart disease in the study population. . . . other factors such as diet and exercise might differ in families with and without smokers; we cannot ignore the possibility that such differences could influence our findings. (p. 921)

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4. No data were available for ETS exposure outside the home.

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Original Contributions

HEART DISEASE MORTALITY IN NONSMOKERS LIVING WITH SMOKERS

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Helsing, K. J. (The Johns Hopkins Training Center for Public Health Research, Hagerstown, MD 21740), D. P. Sandler, G. W. Comstock, and E. Chee. Heart disease mortality in nonsmokers living with smokers. *Am J Epidemiol* 1988;127:915-22.

A private census of Washington County, Maryland, in 1963 obtained information on smoking habits of all adults in the census, and death certificates of all residents who died in the next 12 years were coded for underlying cause of death and matched to the census. Among the white population aged 25 and over, 4,162 men and 14,873 women had never smoked. In this group, death rates from arteriosclerotic heart disease were significantly higher among men (relative risk (RR) = 1.31, 95% confidence interval (CI) 1.1-1.6) and women (RR = 1.24, 95% CI 1.1-1.4) who lived with smokers in 1963, after adjustment for age, marital status, years of schooling, and quality of housing. Among women, the relative risk increased significantly ($p < 0.005$) with increasing level of exposure; among men, there was little evidence of a dose-response relation. The relative risks for nonsmokers who lived with smokers were greatest among both men and women who were younger than age 45 in 1963, but the number of deaths in these groups was small, and confidence intervals were broad. These results suggest a small but measurable risk for arteriosclerotic heart disease among nonsmokers who live with smokers.

heart diseases; smoking; tobacco smoke pollution

The association of cigarette smoking with arteriosclerotic heart disease deaths is well-known (1), and it is now increasingly suspected that the presence of smoke in the

environment may pose a risk to non-smokers. Evidence on the possible association of what is called passive smoking with arteriosclerotic heart disease is as yet far from conclusive, and both the Surgeon General's recent report (2) and that of the National Research Council of the National Academy of Sciences (3) emphasize the need for additional studies. As pointed out by the Surgeon General, because heart disease is so prevalent, even a small increase in risk associated with passive smoking could have a substantial public health impact.

Some epidemiologic studies have been conducted concerning the possible association of arteriosclerotic heart disease with passive smoking. A recent case-control study by Lee et al. (4) reported no consistent evidence of greater passive smoke ex-

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posure among 118 hospitalized nonsmoking cases than among nonsmoking controls hospitalized for reasons considered unrelated to smoking. Gillis et al. (5) reported results of up to 10 years of follow-up for 8,128 Scottish adults aged 45-64 years who participated in a multiphasic health screening exam and for whom smoking history of a spouse or partner was known. At the initial examination, nonsmoking women who lived with smokers had slightly more cardiovascular symptoms such as angina or abnormal electrocardiogram than nonsmokers who were not exposed. No such excess was reported for men. At follow-up, death rates from myocardial infarction for nonsmoking men and women married to smokers were midway between rates for nonexposed and those for active smokers. The number of observed deaths was small, and differences were not statistically significant. Garland et al. (6, 7) reported a dose-response relation in women aged 50-79 years between the amount their husbands smoked and death rates from ischemic heart disease, but the number of deaths was small, and the differences were less than statistically significant, despite a relative risk of 2.7. Hirayama (8) reported in his 15-year prospective study that there was a significantly higher risk of ischemic heart disease among Japanese women whose husbands smoked as compared with those whose husbands did not smoke, as well as a significant dose-response relation with amount smoked. Svendsen et al. (9), in the Multiple Risk Factor Intervention Trial prospective study, found that nonsmoking men whose wives smoked had roughly twice the risk of coronary heart disease morbidity and mortality compared with those whose wives did not smoke. Of particular interest is their finding of no difference between the two groups in blood pressure or cholesterol levels.

Data from a private census conducted in 1963 and other records available in Washington County, Maryland, were used to evaluate the heart disease risk associated with household smoke exposure among

nonsmoking adults. The results of this 12-year follow-up study are reported here.

MATERIALS AND METHODS

In July 1963, a private census obtained data on an estimated 98 per cent of the households in Washington County, Maryland. Information included sex, age, race, marital status, years of schooling, and housing characteristics for all 91,909 individuals enumerated. Information on cigarette, cigar, and pipe smoking habits as well as frequency of church attendance was recorded for each household member aged 16½ or older as of July 15, 1963. A follow-up of a 5 per cent sample of the households in the 1963 census was conducted in 1971 in order to assess the probability of still living in Washington County after eight years. Since age, marital status, years of schooling, and frequency of church attendance were the only characteristics that showed significant association with remaining in the county, a probability of remaining in the county was calculated for each adult in the census aged 25 and over based on those factors and was entered on the census tape. These probabilities allow the population remaining in the county to be estimated at any point in the eight-year period. Since only about 2 per cent of the noninstitutionalized 1963 population was black, the present study is confined to whites.

All death certificates of Washington County residents who died between July 1963 and July 1975 have been coded as to primary, contributing, and underlying causes of death without knowledge of census data, and the information was entered on the census tape for decedents who were in the 1963 census. The Seventh Revision of the *International Classification of Diseases* (ICD) (10) was used for coding causes of death; for this study, we used only deaths with underlying causes of death classified as arteriosclerotic heart disease including coronary disease (ICD 420) and other myocardial degeneration (ICD 422). We also analyzed deaths for which arteriosclerotic

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heart disease was listed on the death certificate but not coded as the underlying cause of death to confirm that similar associations were observed. The category other myocardial degeneration was included because many physicians in this community refer to deaths due to coronary artery disease as arteriosclerotic cardiovascular disease, which is classified under ICD 422.

For the current study, all adults were assigned smoking contribution scores (table 1) ranging from 0 to 12 based on their reported smoking histories—never smoked, present or ex-smoker of cigarettes, cigars, or pipe, and amount smoked. In general, current smokers were assigned scores that were twice those of ex-smokers of like amount. The only exception to this was for persons who only smoked a pipe and/or cigars; census data did not distinguish between current or past pipe or cigar smokers. When pipe and/or cigar smokers also currently smoked cigarettes, however, they were assumed to be current pipe and/or cigar smokers. The contribution to household exposure of only pipe and/or cigar smoke was treated as less than that of current smokers of fewer than 10 cigarettes. Although the household exposure from a pipe or cigar may equal or exceed that from a cigarette, it was arbitrarily assumed that cigar or pipe smokers who never smoked cigarettes would, in general, smoke fewer pipes or cigars per day than light cigarette smokers. Only 9 per cent of spouses of

nonsmoking females smoked only pipes and/or cigars. Thus, the impact of this arbitrary ranking of pipe and cigar smokers and current light smokers is not likely to be large. A household exposure score was calculated as the sum of the contributions of all persons living in that household, and each person's passive smoke exposure score is the household score minus his or her own contribution to it.

A housing index (ranging from 0 to 10) based on running water, number of bathrooms, type of heating system, cooking fuel, and availability of telephone is a rough indicator of quality of housing. In the absence of solid data on household income, the housing index acts as a surrogate measure, particularly to identify the very low-income households.

Among the 22,973 white men and 25,369 white women aged 25 and over in the 1963 census, 4,162 men and 14,873 women reported that they had never smoked. The calculated 1969 midpoint remaining population of these nonsmokers, based on the 1971 follow-up, was 3,454 men and 12,345 women; these constitute the population of interest for this study.

Death rates were calculated as deaths in 12 years per 1,000 midpoint population, adjusted for age, housing quality, marital status, and years of schooling by the binary variable multiple regression procedure described by Feldstein (11) and adapted for epidemiologic use by Shah and Abbey (12).

RESULTS

Table 2 shows the characteristics of the Washington County white population aged 25 and older originally listed in the 1963 census and the percentage in each category reporting that they had never smoked. As was characteristic of that period, relatively few men but more than half the women had never smoked. Among men, there was a slight tendency for the better educated to have a higher percentage of nonsmokers, a trend opposite to that among women.

Characteristics of the population of interest for this study, those who never

TABLE 1
Calculation of each person's contribution to smoke exposure in the home

Smoking status	Ex-smoker	Current smoker
Never smoked	0	0
Cigars and/or pipe only*	1	1
Cigarettes		
<10/day	1	2
10-20/day	3	6
21+/day	5	10
If cigars and/or pipe in addition to cigarettes, add	1	2

* Census data did not distinguish between ex- and current pipe or cigar smokers.

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TABLE 2
Percentage of original census population who reported they had never smoked, by demographic characteristics, whites aged ≥ 25 years, Washington County, MD, 1963

Characteristic	Men		Women	
	No.	% never smoked	No.	% never smoked
Total	22,973	18.1	25,369	58.6
Age (years)				
25-44	10,928	16.5	11,652	46.7
45-54	5,104	16.1	5,378	53.3
55-64	3,631	17.2	4,001	70.1
65+	3,310	27.6	4,338	86.6
Marital status				
Married	19,699	17.4	18,704	55.4
Other	3,274	22.4	6,665	67.6
Grades of school completed				
0-8*	9,977	19.1	9,929	68.5
9-11	4,527	13.1	5,497	52.4
12	5,256	19.1	6,802	54.4
13+	3,213	20.4	3,141	47.6
Housing index				
0-7	4,591	15.9	4,512	59.9
8-10	18,382	18.7	20,857	58.4

* Includes participants for whom grades of school completed was not known.

smoked, are listed in table 3, which shows the calculated midpoint populations in 1969 and the percentage of each group exposed to tobacco smoked by others in the household. For both men and women, the percentage exposed to environmental smoke in the home tends to drop with increasing age and with higher quality of housing. There is, however, a sex difference in the association of education with percentage exposed, nonsmoking men showing slightly increased exposure with more years of schooling and nonsmoking women showing a slight trend in the opposite direction. In addition, married men are less likely and married women more likely to be exposed to the smoke of others in the home.

Table 4 shows the adjusted rates of death from arteriosclerotic heart disease (ICD 420 and 422) in the 12-year period 1963-1975 among men and women who never smoked, according to their level of passive smoke exposure at home. The overall rates are adjusted for age, quality of housing, marital status, and years of schooling. For men, the relative risk for those with some household exposure compared with the

nonexposed is statistically significant (relative risk (RR) = 1.31, 95 per cent confidence interval (CI) 1.1-1.6), but the trend with increasing exposure is negligible. For women, both the difference between the exposed and nonexposed (RR = 1.24, 95 per cent CI 1.1-1.4) and the trend of increasing mortality with increasing levels of exposure in the home (Cochran chi-square = 9.2, $p < 0.005$) are statistically significant. The balance of table 4 presents the adjusted arteriosclerotic heart disease mortality rates for each age group by level of smoke exposure at home. The age group 25-44 years shows the highest relative risks for both men and women, but because of the very small numbers, the 95 per cent confidence limits are quite broad. Nevertheless, it is worthy of note that seven of the eight age-sex groups show increased risk of arteriosclerotic heart disease deaths with passive smoke exposure in the home, and five of the eight indicate a trend with increasing level of exposure.

Results have been shown only for heart disease deaths that were classified as underlying cause of death. Although not

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TABLE 3

Distribution of midpoint population of whites aged ≥ 25 years who never smoked, by sex, percentage exposed to smoke at home, and demographic characteristics, Washington County, MD, 1963-1975

Characteristic	Men		Women	
	No.	% exposed in the home	No.	% exposed in the home
Total	3,454	29.5	12,345	65.5
Age (years) in 1963				
25-44	1,502	30.0	4,618	72.0
45-54	731	34.3	2,553	72.1
55-64	554	28.2	2,472	62.8
65+	667	24.4	2,702	50.5
Marital status				
Married	2,929	27.2	9,033	75.7
Other	525	42.7	3,312	37.5
Grades of school completed				
0-8*	1,578	27.0	5,589	62.7
9-11	504	29.4	2,455	70.0
12	862	31.7	3,158	68.6
13+	510	34.1	1,143	60.6
Housing index				
0-7	594	33.7	2,238	68.2
8-10	2,860	28.7	10,107	64.9

* Includes participants for whom grades of school completed was not known.

shown, death rates and relative risks were also calculated for heart disease deaths coded as a primary cause or a contributing cause of death. A total of 461 nonsmoking men and 1,281 nonsmoking women had arteriosclerotic heart disease listed on the death certificate. Of these, 80 per cent of men and 77 per cent of women were considered to have heart disease as the underlying cause of death. Results were similar whether or not heart disease was considered by the nosologist to be the underlying cause of death. For example, the adjusted relative risk among exposed nonsmoking women compared with nonexposed women was 1.2 for heart disease listed anywhere on the death certificate and 1.1 when heart disease was on the death certificate but not considered to be the underlying cause of death. For males, the corresponding relative risks were 1.3 and 1.4.

DISCUSSION

The findings of this study tend to confirm those of Hirayama (8), whose relative risk from ischemic heart disease was 1.3 for nonsmoking women married to smokers;

our relative risks, however, are considerably lower than those of Garland et al. (7) and Svendsen et al. (9) and higher than those of Lee et al. (4).

There are a number of strengths in this study. Information on smoking was collected for each person in 1963, and follow-up procedures were the same for everyone. Some potential biases were thus avoided: those involved in asking people (or their family members) about prior smoking habits after an illness or death, when recall may be colored by an unconscious search for any possible cause of the illness, and those involved in selecting controls from hospital populations. Furthermore, smoking histories were recorded prior to publication in 1964 of the Surgeon General's first report on smoking and health (13) and the subsequent increase in concern about smoking.

Obviously, the home is not the only place where nonsmokers may be exposed to tobacco smoke. Any association of household passive smoke exposure with heart disease mortality may, in this study, appear weaker than the actual association to the extent

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TABLE 4
Deaths from arteriosclerotic heart disease among nonsmokers exposed or not exposed to tobacco smoke in the home, adjusted* rates per 1,000 population, relative risks, and 95 per cent confidence intervals, Washington County, MD, 1963-1975

Age (years) in 1963	Passive smoking score	Men					Women				
		Midpoint no.	Deaths	Adjusted rate	Relative risk	95% confidence interval	Midpoint no.	Deaths	Adjusted rate	Relative risk	95% confidence interval
All ages	0	2,434	248	98.1	1.00		4,299	437	89.2	1.00	
	1+	1,020	122	128.5	1.31	1.1-1.6	6,096	651	85.8	1.24	1.1-1.4
	1-5	498	58	135.9	1.38	1.1-1.8	3,412	252	83.0	1.20	1.0-1.4
	6+	561	86	122.5	1.25	1.0-1.6	4,674	299	87.8	1.27	1.1-1.5
25-44	0	1,052	4	3.2	1.00		1,291	1	1.1	1.00	
	1-5	211	1	5.7	1.76	0.3-10.6	1,286	3	2.4	2.16	0.4-12.6
	6+	239	4	16.4	6.70	1.6-21.4	2,041	6	3.7	3.36	0.7-16.3
45-64	0	480	30	62.0	1.00		713	8	8.9	1.00	
	1-5	109	8	75.4	1.22	0.6-2.5	701	8	13.2	1.48	0.6-3.9
	6+	142	10	70.6	1.14	0.6-2.2	1,139	16	14.4	1.62	0.7-3.9
65-84	0	396	61	129.2	1.00		919	75	79.2	1.00	
	1-5	65	9	160.1	1.16	0.6-2.2	728	52	74.8	0.94	0.7-1.3
	6+	91	16	162.9	1.26	0.7-2.1	826	63	76.0	0.96	0.7-1.3
85+	0	604	163	330.0	1.00		1,336	363	249.9	1.00	
	1-5	74	36	503.4	1.53	1.2-2.0	897	189	302.2	1.21	1.0-1.4
	6+	89	36	376.7	1.14	0.8-1.5	669	212	313.1	1.26	1.1-1.4

* Adjusted for effects of age (where applicable), marital status, years of schooling, and quality of housing.

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that some of those presumed to have zero or moderate exposure at home were actually subjected to moderate or heavy passive smoke at work or elsewhere outside the home. In this population and during the years of the study, among women aged 25 and over, about 50 per cent were nonworking housewives who would be less likely to be exposed to tobacco smoke outside the home than men, the vast majority of whom were employed. This may in part explain the greater consistency over age groups among women than among men in the increase in relative risk with indicated level of exposure.

All smoking data were obtained in the 1963 census, so no provision can be made for changes in smoking habits which we know took place as a result of publicity about health effects of smoking. Data from a 1975 private census replicating the 1963 census show that the percentage of current cigarette smokers in the 40- to 49-year age range, for example, dropped from 78 per cent to 44 per cent among men and from 50 per cent to 36 per cent among women. On the whole, then, our household passive smoke exposure scores based on 1963 census data will tend to be higher than the actual exposures in later years and to that extent may exaggerate the amount of exposure required to match with a given risk of death from arteriosclerotic heart disease. We also have no data on changes in the household composition which may have occurred prior to or after 1963. Thus, we implicitly assume that any such changes occurred randomly in the population.

We have very little data on other risk factors for arteriosclerotic heart disease in the study population. We have tried to adjust for some: smoking, by restricting the study to nonsmokers; age and sex, by assessing the risk separately for eight age-sex groups; and housing quality, marital status, and years of schooling, by binary variable multiple adjustment. A final check by multiple logistic and Poisson regression adjustment gave virtually identical results. Two

other studies encourage us to disregard hypertension and cholesterol as possible confounding factors. The Garland et al. (6, 7) study showed no significant differences in systolic blood pressure, obesity index, and plasma cholesterol between women married to present or ex-smokers and those married to men who never smoked. Similarly, the Svendsen et al. (9) study showed no significant difference in blood pressure and serum cholesterol between men whose wives smoked and those whose wives were nonsmokers. However, other factors such as diet and exercise might differ in families with and without smokers; we cannot ignore the possibility that such differences could influence our findings.

In summary, this 12-year study of a non-smoking population of white men and women aged 25 and over suggests that non-smokers who live with smokers are at a higher risk of death from arteriosclerotic heart disease than those who live with non-smokers. It seems reasonable to suppose that tobacco smoke is a factor in the increased risk.

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Hirayama, T., "Lung Cancer in Japan: Effects of Nutrition and Passive Smoking." In: Lung Cancer: Causes and Prevention. M. Mizell and P. Correa (eds.). New York, Verlag Chemie International, Chapter 14, 175-195, 1984.

This was a prospective study of a large group of men and women from aged 40 and over in Japan. The participants were first surveyed in 1965 and then followed from 1966 through 1981. Of a total of 265,118 people in the study, 91,540 were nonsmoking women. These were classified according to the smoking habits of their husbands. Over the course of the follow-up, a total of 494 nonsmoking women died from ischemic heart disease, based on which a statistically significant relative risk of 1.31 was reported for women whose husbands smoked 20 or more cigarettes per day compared to women married to nonsmokers. The Hirayama study also reports statistically significant elevations in the lung cancer rates of nonsmoking women married to smokers.

Criticisms

1. Important potential risk factors for heart disease were not controlled, such as systolic blood pressure and plasma cholesterol.
2. No information was collected on ETS exposure outside of the home, such as in the workplace or elsewhere.
3. The study involved a disproportionately large number of individuals of lower socioeconomic status. In Japan, there are

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socioeconomic differences in the use of charcoal or kerosene stoves and other cooking habits, which may involve exposure which could confound any possible effects of ETS.

4. The population studied was unrepresentative of Japanese society, in that it was based primarily on an agricultural population.

5. Inaccuracies in estimates of ETS exposure may have occurred from potential misclassification of the wives' smoking habits.

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Lung Cancer:

Causes and Prevention

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Lung Cancer In Japan: Effects of Nutrition and Passive Smoking

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ABSTRACT

Lung cancer is on a sharp increase in both men and women in Japan. Nonsmoking wives with smoking husbands were found to carry an elevated risk of lung cancer and ischemic heart disease by a large-scale cohort study, 1966-1981, for 265,118 adults in 29 Health Center Districts in Japan, the risk steadily going up with the increase in number of cigarettes smoked by the husband. In major cancers other than lung, no such risk elevation was observed. A nonsmoking husband with a smoking wife also showed an elevated risk of lung cancer. The risk-reducing effect of daily intake of green-yellow vegetables on lung cancer was observed for passive smoking just as for active smoking. Those women eating green-yellow vegetables daily showed a significantly lower risk of lung cancer from the passive influence of their husbands' smoking. Such risk reduction was not observed for ischemic heart disease. The observed results suggest that the influence of husband's smoking on nonsmoking wives in raising the risk of lung cancer is as a cancer promoter rather than a cancer initiator. This promoter hypothesis may explain why such continuous but low-dose exposure of passive smoking, which starts after adult age is reached, significantly elevates lung cancer risk in nonsmoking wives.

Key Words: Japan, cohort study, passive smoking, lung cancer, ischemic heart disease, green-yellow vegetables, β -carotene, promoter, promoter-inhibitor

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Lung Cancer Causes and Prevention

Introduction

The mortality from lung cancer has been increasing rapidly in Japan (Figure 1). The number of deaths among males was 520 in 1947 and 17,555 in 1982, the corresponding number for females was 248 and 6661.

There exists little sign of a slowing down of the rate of increase, and the number of deaths from lung cancer are expected to exceed the number of deaths from stomach cancer in the near future. In parallel to this trend the number of cigarettes sold in Japan also has been on a sharp rise (Figure 1). The random sample survey conducted by the Tobacco Monopoly Corporation in 1982 revealed that currently 70.1% of adult males and 15.4% of adult females smoke in Japan.

The purpose of this chapter is to study the causative factors of lung cancer in Japan with special reference to the effect of passive smoking relative to the effect of active smoking. The possible influence of nutrition, β -carotene-rich green-yellow vegetables in particular, on the risk enhancing effect of active and passive smoking also is studied.

Methods

The materials of our ongoing large-scale cohort study for 265,118 adults aged 40 years and above in Japan were analyzed in detail to discover factors altering the

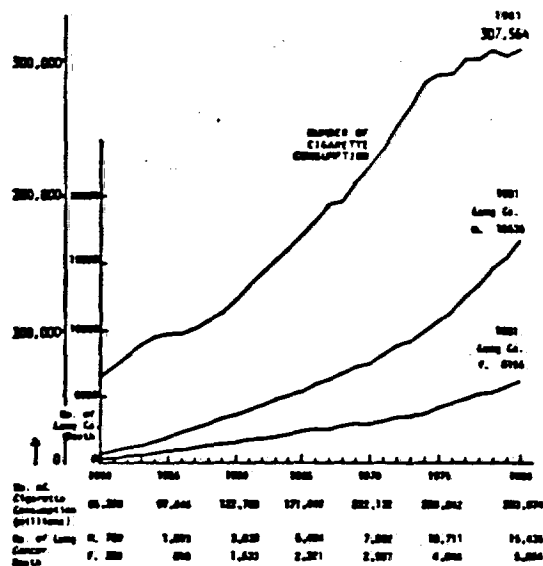


Figure 1. Trends in cigarette consumption and lung cancer deaths in Japan (1950-1981).

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risk of lung cancer in both men and women. For statistical analysis, programs included in the book *Epidemiologic Analysis with a Programmable Calculator* (U.S. Department of Health, Education and Welfare, 1979) mainly were used.

Results

Active Smoking and Lung Cancer Risk

Cigarette smoking was identified by far the most important cause of lung cancer in Japan, both by case-control studies conducted by the author and other researchers and by a large-scale cohort study (1-6) being conducted by the author for 265,118 adults (122,261 men and 142,857 women) aged 40 and above (95% of census population) in 29 Health Center Districts in Japan. These subjects were surveyed in October-December 1965 and followed up from January 1966 until December 1981. A clear-cut dose-response relationship was observed between the number of cigarettes ever smoked and the age-standardized mortality rate of lung cancer. The mortality rate of lung cancer also was found to be higher the earlier smoking was begun when age and total number of cigarettes ever smoked were standardized (Figure 2). The lung cancer-standardized mortality rate was observed

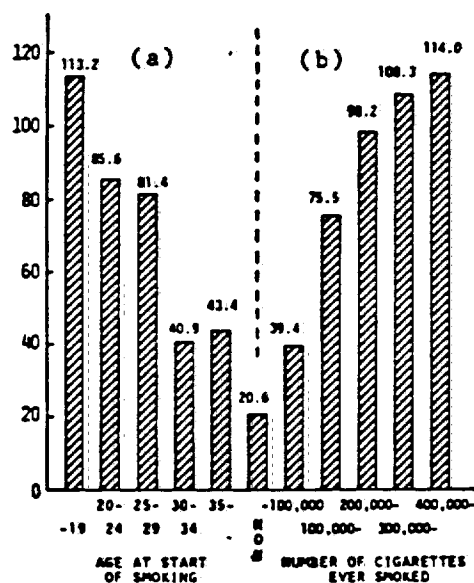


Figure 2. Lung Cancer. (a) Attained age- and amount of smoking-standardized mortality rate by age at start of smoking. (b) Attained age- and age at start of smoking-standardized mortality rate by total amount of cigarettes ever smoked. (Prospective study, 1966-1978 Japan.)

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so be 18.3% lower in smokers who do not inhale compared to regular deep inhalers, and 48.9% lower in smokers of filtertip cigarettes compared to smokers of nonfiltertip cigarettes, according to our cohort study. The risk of lung cancer in daily smokers also was noted to approach gradually that of nonsmokers with the lapse of years after smoking cessation, risk difference diminishing by 41.6% in 5 years after stopping the habit. This strongly suggests the major part of the influence of smoking during adulthood is the promoter action of substances included in mainstream smoke.

Effect of Nutrition on Active Smokers

Daily intake of green-yellow vegetables, rich in β -carotene, was found significantly to lower the risk of lung cancer (7, 8), particularly when the total amount of cigarettes ever smoked was less than 300,000 (6) (Figure 3). No other dietary habit showed such risk reduction. Risk reduction after smoking cessation appeared to be more pronounced in case of daily consumers of green-yellow vegetables. Taking similar evidence in laboratory studies into consideration, a promoter-inhibitor interaction model was conceptualized.

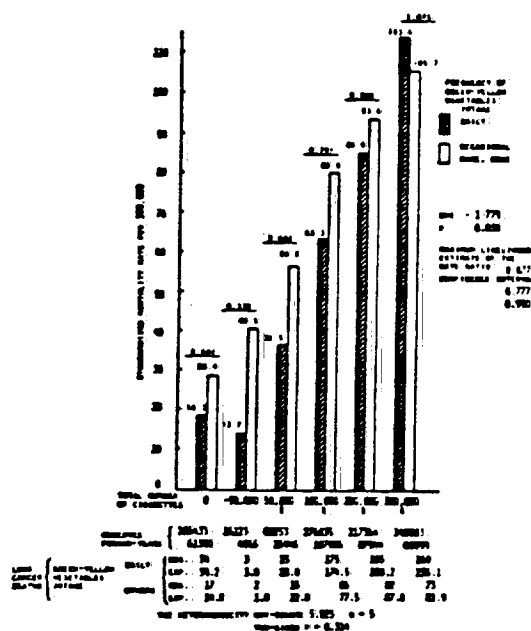


Figure 3. Standardized mortality rate for lung cancer by total number of cigarettes ever smoked and by frequency of green-yellow vegetable intake; males. (Prospective study, 1966-1978.)

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Passive Smoking and Lung Cancer

In the present cohort study (1966-1981), 427 deaths from lung cancer in women were recorded during 16 years of followup (1966-1981). Of these women, 269 were married, and 200 of these also were nonsmokers. These cases occurred among 91,540 nonsmoking married women whose husbands' smoking habits were studied. The risk of lung cancer was carefully measured, taking into consideration possible confounding variables. There was a statistically significant increased risk in relation to the extent of the husband's smoking (Figure 4), which confirmed the validity of previous reports (9, 10). The association was significant when observed by age of husbands (Table 1, Figures 1 and 5) and also by age of wives (Table 2). The further detailed analysis on materials cross-tabulated by age and occupation of the husband also confirmed the association (Table 3). The husband's drinking habits were noted to have no effect in raising the risk of lung cancer in nonsmoking wives (Table 4).

Similar significant risk elevation of lung cancer with the increase in the extent of husband's smoking also was observed with ischemic heart disease when observed by husband's age and occupation (Tables 5 and 6). The significant risk elevation of cancer of the nasal sinus also was observed in nonsmoking wives with husband's smoking. The risk elevation of emphysema and chronic bronchitis with spouse's smoking also was noted with borderline significance. However there was no tendency of risk elevation at all in major cancers other than lung (total of cancers of stomach, cervix, and breast), the standardized mortality rate in nonsmoking wives being almost exactly the same regardless of the husband's smoking habit (Table 7, Figure 6).

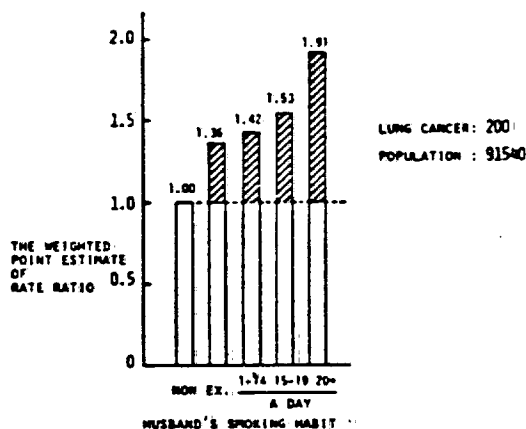


Figure 4. Age-standardized mortality rate ratio for lung cancer in nonsmoking wives by smoking habits of their husbands. (Prospective study, 1966-1981, Japan.)

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Table 1. Mortality rate for lung cancer in women by age group and by smoking habit of husband (patient herself a nonsmoker): prospective study, 1966-1981, Japan^a

Husband's age group	Husband's smoking habit							
	Nonsmoker				Number of cigarettes a day			
	No.		Ex-smoker		1-14/d		15-19/d	
	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.
40-49	4	6,229	1	1,255	8	8,621	6	5,158
50-59	10	7,791	3	1,922	20	9,668	8	4,052
60-69	18	7,120	11	2,687	28	7,243	9	2,513
70-79	5	755	2	348	2	612	1	105
Total	37	21,895	17	6,212	58	26,144	24	11,828
^a The weighted point estimate of rate ratio and test-based 90% confidence limits								
	1.00		2.18	1.36	2.01	1.42	2.38	1.58
			0.85		1.01		0.98	
							2.02	
					1.45		1.04	
Mantel-Haenszel χ^2	—		1.0855		1.8290		3.0295	
one-tail p value			0.1389		0.0337		0.0012	
								Mantel extension χ^2 2.915
								one-tail p value 0.00178

Table 2. Mortality rate for lung cancer in nonsmoking wives by smoking habit of husbands and by age group of wife: prospective study, 1966-1981, Japan^a

Wife's age group	Husband's smoking habit							
	Nonsmoker				Number of cigarettes a day			
	No.		Ex-smoker		1-19/d		20+/d	
	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.
40-49	4	7,918	21	17,492	21	12,615	46	38,025
50-59	14	7,635	46	15,640	31	8,814	91	32,089
60-69	16	6,170	31	10,381	10	3,793	57	20,344
70-79	3	172	1	671	2	239	6	1,082
Total	37	21,895	99	44,184	64	25,461	200	91,540
^a The weighted point estimate of rate ratio and test-based 90% confidence limits								
	1.00		2.01	1.43	2.35	1.74	1.19	
			0.99					
								Mantel extension χ^2 2.424
Mantel-Haenszel χ^2	—		1.6042		2.3731		0.0088	
one-tail p value			0.0543		0.0088			one-tail p value 0.00768

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Table 5. Mortality rate for lung cancer in women by age, occupation, and smoking habit of husbands (patient herself a nonsmoker)^a

Husbands age (year)	Occupation ^b	Nonsmoker		Ex-smoker or 1-19/day		≥ 20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40-49	Total	4	6,229	15	15,034	16	10,764
	1		324		633	1	566
	2		90		231		293
	3	1	908	2	2,247	3	1,867
	4	1	476	1	993		1,044
	5	1	2,502	6	5,941	9	3,636
	6		46		165		108
	7		177	1	486	1	426
	8		1,112	3	3,431	2	2,241
	9		162		345		243
	10	1	432	1	542		340
50-59	Total	10	7,791	31	15,642	24	9,820
	1	1	343		593	2	446
	2		175		233	1	319
	3	1	817	5	1,764	1	1,324
	4	1	653	2	1,133	5	1,092
	5	4	3,497	16	6,812	9	3,514
	6		35		89		50
	7		120		273	1	234
	8	3	1,375	6	3,478	2	2,155
	9		164		378	1	251
	10		610	2	869	2	433
60-69	Total	18	7,120	48	12,443	23	4,631
	1		227	1	327	1	179
	2	1	91		143		124
	3	1	305	2	394	2	327
	4	2	508	5	822	1	500
	5	13	4,084	33	6,845	10	2,152
	6		9		31		14
	7		45		82		55
	8	1	805	5	1,784	4	736
	9		121	1	208		92
	10	1	925	1	1,607	5	472
70 +	Total	5	753	3	1,063	1	226
	1		32		30		5
	2		21		14		4
	3		18	1	36		8
	4		48		73		20
	5	3	323	1	446		89
	6		1		1		0
	7		1		3		1
	8		87	2	119	1	36
	9		11		19		2
	10	2	213	1	322		61
Standardized Risk Ratio		1,000		1,436		1,872	

Maximal extension χ^2 : 3,124; overall p value: 0.00089.

^aOccupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, husbandmen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

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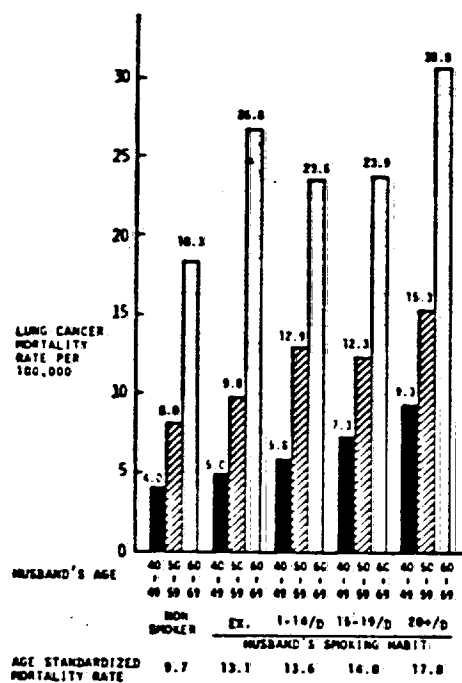


Figure 5. Age-specific mortality rate for lung cancer per 100,000 in nonsmoking wives by smoking habits of their husbands. (Prospective study, 1966-1981, Japan.)

Table 4. Mortality rate for lung cancer in women by age group and by alcohol drinking habits of husband: (patient herself a nonsmoker): prospective study, 1966-1981, Japan

Husband's age group	Husband's drinking habits							
	Nondrinker		Occas. Rare		Daily		Obscure	
	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.
40-49	12	6,141	10	15,877	13	9,935	0	74
50-59	12	7,437	29	14,666	24	10,786	0	364
60-69	23	6,741	35	9,234	27	7,606	4	633
70-79	1	686	5	666	4	589	1	105
Total	48	21,005	79	40,443	68	28,916	5	1,176

The weighted point estimate of rate ratio and test-based 90% confidence limits

Mantel-Haenszel χ^2 one-tail p value

1.00
1.03
0.66
1.61
1.31
0.77
-0.1019
0.4594
0.4564
0.3240

Mantel extension χ^2 0.626 one-tail p value 0.26566

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Table 5. Mortality rate for ischemic heart diseases in women by age group and by smoking habits of husband: prospective study, 1966-1981, Japan

Husband's age group	Husband's smoking habit					
	Number of cigarettes a day					
	Nonsmoker		Ex-smoker		20+/d	
	No.	Pop.	No.	Pop.	No.	Pop.
40-49	13	6,229	40	15,034	33	10,764
50-59	26	7,791	56	15,642	49	9,820
60-69	65	7,120	125	12,443	47	4,651
70-79	14	755	19	1,065	7	226
Total	118	21,895	240	44,184	136	25,461

The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00	1.33 0.91	1.63 1.31 1.06
Mantel-Haenszel χ^2 one-tail p value	—	0.8504 0.1976	2.0723 0.0191
			Mixed extension χ^2 2.073 one-tail p value 0.01909

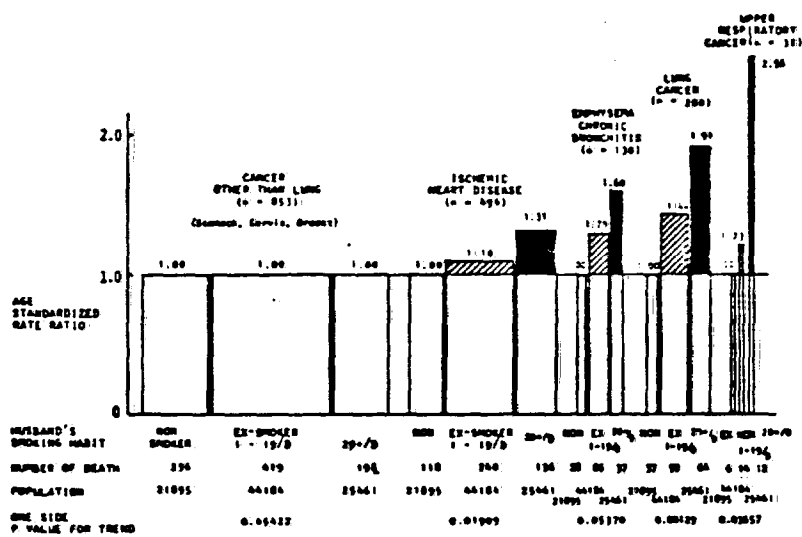


Figure 6. Standardized mortality rate ratio for selected causes of death in 91,540 nonsmoking women by smoking habits of their husbands. (Prospective study, 1966-1981, Japan.)

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Table 6. Mortality rate for ischemic heart disease in women by age, occupation, and smoking habit of husbands (patient herself a nonsmoker)^a

Husband's age (years)	Occupation ^b	Nonsmoker		Ex-smoker or 1-19/day		≥ 20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40-49	Total	13	6,229	40	15,034	33	10,764
	1	1	324		633	1	366
	2		90	1	231		293
	3		908	4	2,247	1	1,867
	4		476	1	993	5	1,044
	5	8	2,502	25	5,941	18	3,636
	6		46		165		108
	7	1	177	2	486		426
	8		1,112	7	3,431	6	2,241
	9		162		345	1	243
	10	3	432		342	1	340
50-59	Total	26	7,791	56	15,642	49	9,820
	1	1	345	3	593		446
	2	2	175		233		319
	3	2	817	5	1,764	6	1,324
	4		633	6	1,133	4	1,092
	5	15	3,497	27	6,812	26	3,514
	6		35	1	89		50
	7		120	1	273	2	234
	8	5	1,375	8	3,478	11	2,155
	9		164	1	378		231
	10	1	610	4	869		435
60-69	Total	65	7,120	125	12,443	47	4,651
	1	2	277	2	577	1	179
	2	1	91	2	145	1	124
	3	2	305	5	594	1	327
	4	10	508	8	822	5	500
	5	36	4,084	79	6,845	27	2,152
	6		9	1	31		14
	7	1	45	1	82	1	35
	8	7	805	13	1,784	6	736
	9	1	121	2	208		92
	10	5	925	12	1,607	5	472
70+	Total	14	755	19	1,065	7	226
	1	2	32	1	30		5
	2	2	21		14	1	4
	3		18	1	36		8
	4	1	46	1	73		20
	5	5	323	11	446	2	89
	6		1		1		0
	7		1		5		1
	8		87	1	119	3	36
	9		11	2	19		2
	10	4	213	2	322	1	61
Standardized Rat. Ratios		1,000		1,103		1,359	

^aOccupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, husbandmen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

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Table 7a. Mortality rates for major cancers other than lung in women by age group and by smoking habit of husband (patient herself a nonsmoker): prospective study, 1966-1981, Japan^a

Husband's age group	Husband's smoking habit (cigarettes a day)							
	Nonsmoker		Ex-smoker 1-19		20+		Total	
	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.
40-49	44	6,229	117	15,034	71	10,764	232	32,027
50-59	97	7,791	191	15,642	119	9,820	407	33,253
60-69	160	7,120	274	12,443	106	4,651	540	24,214
70-79	14	755	20	1,065	8	226	42	2,046
Total	315	21,895	602	44,184	304	25,461	1,221	91,540

^aThe weighted point estimate of rate ratio and two-sided 90% confidence limits

	1.00	1.11	1.05
		0.90	0.95
Mantel-Haenszel χ^2 one-tail p value	—	-0.0015 0.4994	0.0449 0.4821
			Mantel extension χ^2 0.113 one-tail p value 0.4542

Table 7b. Mortality rates for major cancers other than lung in women by age, occupation, and smoking habit of the husband (patient herself a nonsmoker)^a

Husbands age (years)	Occupation ^b	Nonsmoker		Ex-smoker or 1-19/day		≥20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40-49	Total	45	6,229	120	15,034	74	10,764
	1	2	324	1	653	3	566
	2		90	1	231	2	293
	3	9	908	17	2,247	12	1,867
	4	3	476	8	993	8	1,044
	5	17	2,502	59	5,941	35	3,636
	6		46		165		108
	7	1	177	6	486		426
	8	10	1,112	21	3,431	13	2,241
	9	1	162	4	345	1	243
	10	2	432	3	542		340
50-59	Total	98	7,791	195	15,642	122	9,820
	1	13	345	2	593	3	446
	2	2	175	1	253	1	319
	3	14	817	16	1,764	10	1,324
	4	1	653	18	1,135	9	1,092
	5	49	3,497	81	6,812	56	3,514
	6		35		89		50
	7	2	120	4	273	2	234
	8	12	1,375	49	3,478	31	2,155
	9		164	7	378	4	251
	10	5	610	17	869	6	435
60-69	Total	161	7,120	227	12,443	106	4,651
	1	5	227	5	327	2	179
	2	5	91	3	143	3	124
	3	7	305	11	594	5	327
	4	5	508	28	822	12	500
	5	102	4,084	158	6,845	58	2,152

Table 7 b. (cont.)

Husbands age (years)	Occupation ^b	Nonsmoker		Ex-smoker or 1-19/day		≥ 20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
	6		9	1	31		14
	7	1	45	3	82	2	55
	8	10	805	40	1,784	17	736
	9	2	121	3	208		92
	10	24	925	25	1,607	7	472
70 +	Total	14	755	21	1,065	8	226
	1		32		50		5
	2	1	21		14		4
	3	1	18		36		8
	4		48	1	73	2	20
	5	7	323	15	446	4	89
	6		1		1		0
	7		1		5		1
	8	1	87	2	119	1	36
	9		11		19		2
	10	4	215	5	322	1	61
Standardized Risk Ratios		1.000		0.969		1.034	

Mantel extension χ^2 : -0.129, one-tail p value: 0.44868.

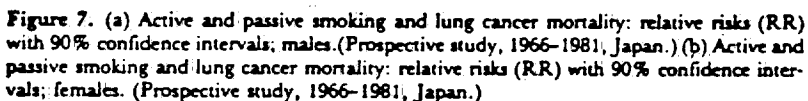
^b Occupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, lumbermen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

Comparison of the Effects of Active Smoking and Passive Smoking

When the risk of lung cancer in nonsmokers with nonsmoking spouses was taken as a unit, a definite dose-response relationship was observed, the highest risk being in heavy active smokers, followed by mild active smokers, then heavy passive smokers, and then mild passive smokers (Figure 7). The risk gradient was similar both in men and in women (Figure 8). A significantly elevated risk of lung cancer also was noted for nonsmoking husbands with smoking wives.

Because the size of population exposed to passive smoking is quite large in the case of women, the effect of passive smoking because of the husband's smoking was estimated as 65% of that of active smoking. Our recent survey showed that 47.5% and 32.6% of Japanese adult women were being exposed to passive smoking at home and at the workplace, respectively (Figure 9). Therefore it must be a sound estimate that the total effect of passive smoking is approximately equivalent to that of active smoking in women. However, as a majority of adult men are still smokers, the total effect of passive smoking relative to active smoking must be on

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Effect of Nutrition on Passive Smokers

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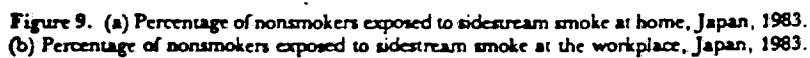
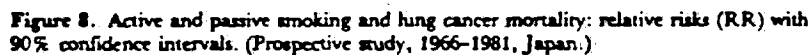


Table 8. Lung cancer mortality rate in nonsmoking wives by smoking habit of the husband: comparison between daily and non daily intake of green-yellow vegetables

Husband's smoking habits		Nonsmoker				Ex-smoker on 1-19 day				≥ 20/day			
Wife's eating habits		Green-yellow vegetables											
		Daily		Nondaily		Daily		Nondaily		Daily		Nondaily	
Husband's		Lung Pop. Ca.		Lung Pop. Ca.		Lung Pop. Ca.		Lung Pop. Ca.		Lung Pop. Ca.		Lung Pop. Ca.	
Occupation	Age												
Agriculture	40-49	1,958	1	544	0	5,050	5	891	1	5,037	7	599	2
	50-59	2,805	4	692	0	5,196	11	1,616	3	2,588	9	926	0
	60-69	3,359	7	725	6	5,106	22	1,739	11	1,588	6	564	4
	70-79	258	3	65	0	287	1	159	0	45	0	44	0
Others	40-49	2,422	3	1,305	0	7,288	8	1,805	1	5,377	5	1,751	2
	50-59	3,181	5	1,113	1	6,732	12	2,098	3	4,633	5	1,673	10
	60-69	2,266	4	770	1	4,088	9	1,510	6	1,906	10	593	3
	70-79	216	2	216	0	371	1	248	3	81	1	56	0
Total		16,465	29	5,430	8	34,118	69	10,066	30	19,255	43	6,206	21
Grand total		Population: 91540						Lung cancer: 200					
Green-yellow vegetables		Mantel-extension χ^2						P-value (two tailed)					
Daily		2.072						0.03827					
Nondaily		2.487						0.01288					
Total		3.090						0.00200					

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Table 9. Effect of daily intake of green-yellow vegetables on lung cancer mortality in nonsmoking wives with smoking husbands^a

Husband's smoking habit		Ex-smoker or 1-19/day		≥ 20/day	
Wife's eating habit		Green-yellow vegetables			
		Daily		Nondaily	
Husband's		Lung Pop. Ca.		Lung Pop. Ca.	
Occupation	Age	Lung Pop. Ca.		Lung Pop. Ca.	
Agriculture	40-49	5,050	5	891	1
	50-59	5,196	11	1,616	5
	60-69	5,106	22	1,739	11
	70-79	287	1	159	0
Others	40-49	7,288	8	1,805	1
	50-59	6,732	12	2,098	3
	60-69	4,088	9	1,510	6
	70-79	371	1	248	3
Total		34,118	69	10,066	30
				19,255	43
					6,206
					21

^aMantel-Haenszel χ^2 = 1.986, *p* (two-tailed) 0.047. Odds ratio: Nondaily green-yellow vegetable eater, 1.000; daily green-yellow vegetables intake, 0.707 (standardized rate ratio); 90% confidence limits, 0.538-0.943.

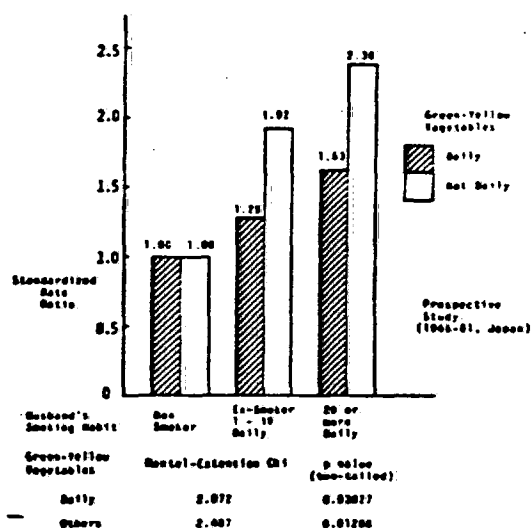


Figure 10. Lung cancer mortality ratio in nonsmoking wives by smoking habits of their husbands. Comparison between daily and nondaily intake of green-yellow vegetables.

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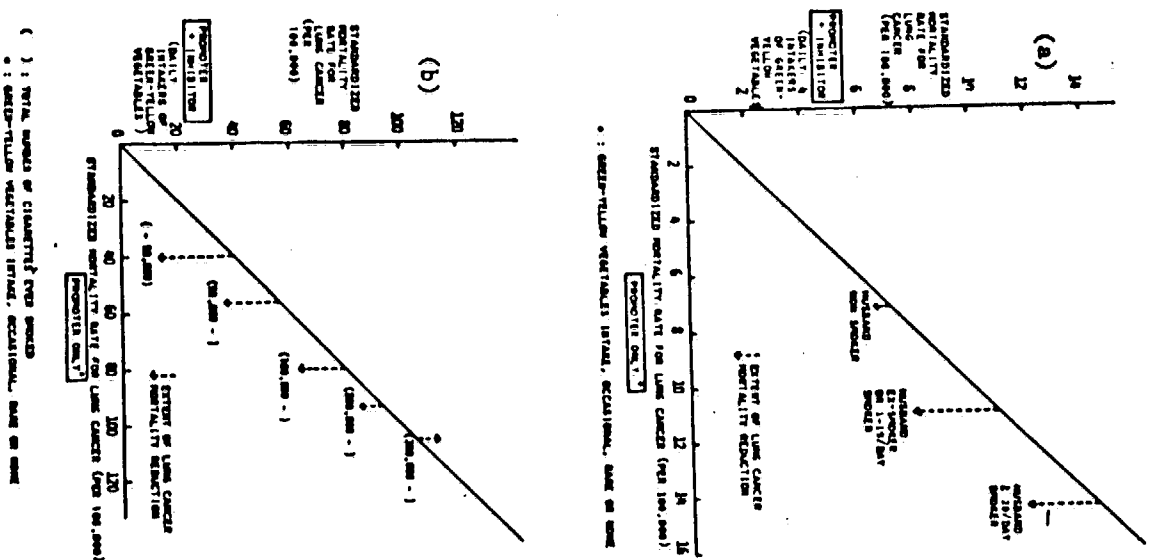


Figure 11. (a) Standardized mortality rate for lung cancer in nonsmoking wives by smoking habit of the husband. Comparison between daily and nondaily intake of green-yellow vegetables. (Prospective study, 1966-1981, Japan.) (b) Standardized mortality rate for lung cancer according to total number of cigarettes smoked and frequency of consumption of green-yellow vegetables, males. (Prospective study, 1966-1978, Japan.)

Table 10. Ischemic heart disease mortality rate in nonsmoking wives by smoking habit of the husband: comparison between green-yellow vegetables intake daily and nondaily

Husband's smoking habit		Nonsmoker				Ex-smoker or 1-19/day				≥ 20/day			
Wife's eating habit		Green-yellow vegetables											
		Daily		Nondaily		Daily		Nondaily		Daily		Nondaily	
Husband's		Ischemic Pop.		Ischemic Heart D.		Ischemic Pop.		Ischemic Heart D.		Ischemic Pop.		Ischemic Heart D.	
Occupation	Age												
Agriculture	40-49	1,958	6	544	2	3,050	18	891	7	3,037	14	599	4
	50-59	2,805	11	692	4	5,196	25	1,616	2	2,588	21	926	5
	60-69	3,359	30	725	6	5,106	55	1,739	24	1,588	21	564	6
	70-79	258	2	65	3	287	10	159	1	45	2	44	0
Others	40-49	2,422	5	1,305	2	7,288	10	1,805	5	5,377	12	1,751	3
	50-59	3,181	8	1,113	3	6,732	18	2,098	11	4,633	17	1,673	6
	60-69	2,266	21	770	8	4,088	33	1,510	13	1,906	11	593	9
	70-79	216	7	216	2	371	6	248	2	81	3	56	2
Total		16,465	88	5,450	30	34,118	175	10,066	65	19,255	101	6,206	35
Grand total		Population: 91540						Ischemic heart disease: 494					
Green-yellow vegetables		Mantel-extension χ^2						P value (two tailed)					
Daily		2.307						0.02105					
Nondaily		0.820						0.41222					
Total		2.406						0.01615					

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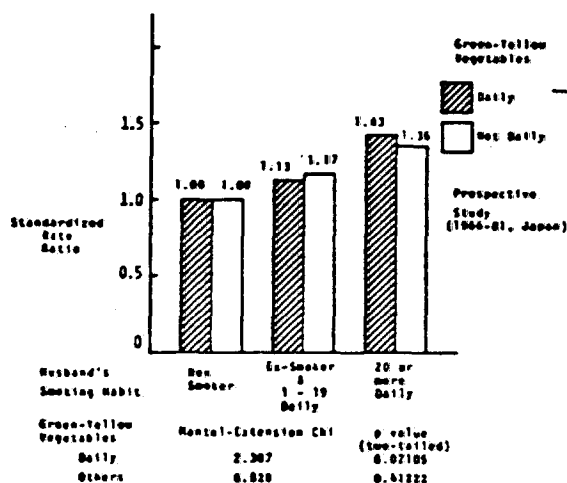


Figure 12. Ischemic heart disease mortality ratio in nonsmoking wives by smoking habits of their husbands. Comparison between daily and nondaily intake of green-yellow vegetables.

Discussion

The age-adjusted mortality rates for lung cancer have been sharply increasing both for men and for women in Japan. As only a fraction of Japanese women with lung cancer smoke cigarettes, the reasons for the trend of their mortality from lung cancer have been unclear. The present study appears to explain at least a part of this long-standing riddle.

This observation also questions the validity of the conventional method of assessing the relative risk of developing lung cancer in smokers by comparing them with nonsmokers. This study shows that nonsmokers are not a homogeneous group and should be subdivided according to the extent of previous exposure to indirect or passive smoking. Although the relative risk of indirect smoking was smaller than that of direct smoking, the absolute excess deaths from lung cancer resulting from passive smoking must be important because of the large size of the exposed group. Therefore, these results of our current study must be of public health importance, strengthening already existing evidence for a health hazard from passive smoking (11-13) (Table 11).

As shown in Figure 9, 47.5% and 32.6% of 158 nonsmoking adult women surveyed recently are noted to be exposed to sidestream smoke at home and at the workplace, respectively. One survey conducted in Aichi prefecture in Japan showed that nonsmoking wives are exposed to their husband's smoking 6.7 times a day on the average.

Because sidestream smoke contains varieties of cancer promoters at higher concentration than does mainstream smoke, it must be reasonable to consider the

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Table 11. Passive smoking is hazardous to health

1. Existence of toxic substances (including carcinogens) in sidestream smoke mostly at higher concentration than in mainstream smoke.
2. Existence of a large number of nonsmokers who have to inhale sidestream smoke frequently and intensively for long years at home and/or at the workplace.
3. Existence of sidestream smoke component in blood and urine of nonsmokers exposed to passive smoking (eg, nicotine, CO-Hb in blood and Mutagens in urine.).
4. Existence of functional abnormalities in nonsmokers exposed heavily to passive smoking (eg, respiratory or circulatory function).
5. Lung tissue damage and destruction in chronic passive smokers as shown by elevated hydroxyproline excretion in urine.
6. Higher incidence of selected diseases in nonsmokers exposed heavily to passive smoking (eg, pneumonia, bronchitis, asthma, ischemic heart disease, lung and nasal sinus cancer).
7. Experimental evidence.

main effect of passive smoking on lung cancer risk results from the prolonged exposure to such promoters in sidestream smoke. The risk-inhibitory effect of a daily intake of green-yellow vegetables that are rich in β -carotene must be considered as an additional evidence for such a promoter action hypothesis of passive smoking. The hypothesis also explains why exposure to passive smoking that starts after reaching adult age can significantly influence the risk of lung cancer.

The histology of 21 cases of lung cancer in nonsmoking wives of smoking husbands was not essentially different from that in smoking women (adenocarcinoma 57.1%, squamous cell carcinoma 19.0%, and small-cell carcinoma 4.8%). A case-control study conducted within our cohort study revealed a significant dose-response relationship between adenocarcinoma of the lung and the number of cigarettes smoked daily, relative risk being 1.39 and 5.75 for smokers of 1-14 and 15 or more cigarettes daily, the chi square for the trend being 6.848 with a one-tail p value of 0.004. Therefore the predominance of adenocarcinoma of the lung in nonsmoking women with smoking husbands should not be considered unfavorable evidence for promoter action hypothesis of passive smoking. In passive smoking, sidestream smoke usually is inhaled through the nose, whereas in active smoking mainstream smoke always is inhaled through the mouth. This difference could be a reason for the elevated risk of nasal sinus cancer in passive smokers. The mechanism of the action of passive smoking on the risk of ischemic heart disease, however, must be explained in different ways (eg, a combined action of carbon monoxide and nicotine).

In summary, to reduce the effect of active and passive smoking and to encourage the effect of nutrition, in particular β -carotene intake, would be the most productive course for lung cancer prevention. For selected persons exposed to other known carcinogens, eg, those related to occupation or radiation, such environmental exposure also must be minimized in addition to the preventive measures focused on lifestyle variables given above.

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Hole, D.J., Gillis, C.R., Chopra, C. and Hawthorne, V.M., "Passive Smoking and Cardiorespiratory Health in a General Population in the West of Scotland," British Medical Journal 299: 423-427, 1989.

The report is a follow-up of the 1984 Gillis, et al. paper dealing with a prospective study of the residents of two urban areas in the west of Scotland. The subjects were healthy middle-aged men and women, first surveyed between 1972 and 1976, and then followed-up for an average of 11.5 years. Based on 84 deaths, a relative risk of ischemic heart disease mortality of 2.01 was reported. This was based on combined data from both men and women, and was reported as statistically significant.

Data were also reported concerning a variety of cardiovascular and respiratory symptoms, as well as all cause and lung cancer mortality. For each of these, the relative risks were reported to be consistently above 1.0, although other than for ischemic heart disease, none were reported as statistically significant. In computing relative risks, age, sex, social class, blood pressure, cholesterol and body mass were taken into account.

Criticisms

1. Although the authors report an attempt to control for several potential confounding variables, a number of factors were not controlled, such as outdoor air pollution, the presence of molds or dampness in the home, the use and type of heating fuels, diet, heredity, and many other factors.

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2. This study is merely an update of the Gillis, et al. (1984) report. Thus, if a tally were being made of the studies dealing with ETS and heart disease, it would be inappropriate to include both studies, since in a sense this would be like listing the same data twice.

3. The authors also report data comparing smokers married to nonsmokers versus smokers married to other smokers. Although not statistically significant, the relative heart disease risk reported for smokers living with a smoker was less than the risk reported for a smoker living with a nonsmoker.

4. The heart disease relative risk reported for ETS exposure was 2.01. This is to be compared to 2.27 that the authors report as the relative risk for smokers compared to nonsmokers. Even the authors question whether this is "biologically plausible."
(p. 426)

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Passive smoking and cardiorespiratory health in a general population in the west of Scotland

David J Hole, Charles R Gillis, Carol Chopra, Victor M Hawthorne

Abstract

Objective—To assess the risk of cardiorespiratory symptoms and mortality in non-smokers who were passively exposed to environmental smoke.

Design—Prospective study of cohort from general population first screened between 1972 and 1976 and followed up for an average of 11.5 years, with linkage of data from participants in the same household.

Setting—Renfrew and Paisley, adjacent burghs in urban west Scotland.

Subjects—15 399 Men and women (80% of all those aged 45-64 resident in Renfrew or Paisley) comprised the original cohort; 7997 attended for multiphasic screening with a cohabitee. Passive smoking and control groups were defined on the basis of a lifelong non-smoking index case and whether the cohabitee had ever smoked or never smoked.

Main outcome measure—Cardiorespiratory signs and symptoms and mortality.

Results—Each of the cardiorespiratory symptoms examined produced relative risks >1.0 (though none were significant) for passive smokers compared with controls. Adjusted forced expiratory volume in one second was significantly lower in passive smokers than controls. All cause mortality was higher in passive smokers than controls (rate ratio 1.27 (95% confidence interval 0.95 to 1.70)), as were all causes of death related to smoking (rate ratio 1.30 (0.91 to 1.85)) and mortality from lung cancer (rate ratio 2.41 (0.45 to 12.83)) and ischaemic heart disease (rate ratio 2.01 (1.21 to 3.35)). When passive smokers were divided into high and low exposure groups on the basis of the amount smoked by their cohabitees those highly exposed had higher rates of symptoms and death.

Conclusion—Exposure to environmental tobacco smoke cannot be regarded as a safe involuntary habit.

of lung cancer; it overcomes many of these criticisms. The survey prospectively studied a general population aged 45-64 years, and the collected data allowed participants from the same household to be identified. The measure of exposure to environmental tobacco was obtained directly from cohabitees and did not rely on self reporting. Data on prevalences of symptoms of respiratory and cardiovascular disease, forced expiratory volume in one second, mortality, and incidence of cancer are all available for this population. The findings reported here update an earlier report; it adds 567 further deaths to the previous findings¹ and extends the range of baseline measurements to include forced expiratory volume in one second. Confounding variables such as social class, blood pressure, cholesterol concentration, body mass index, and social class have been allowed for in calculating relative risks for passive smokers.

Subjects and methods

This general population cohort comprises all men and women aged 45-64 years resident in the towns of Renfrew and Paisley in the west of Scotland between 1972 and 1976.¹ Eligibility was established by a door to door census of all households in the two towns. Everyone who met the age and residency criteria was invited to attend one of 12 temporary centres for a multiphasic cardiorespiratory screening examination.¹ Between 1972 and 1976, 15 399 residents (an 80% response) completed a standardised self administered questionnaire that included questions on smoking behaviour and was checked by experienced interviewers when subjects attended for screening. Respiratory symptoms were assessed with the Medical Research Council's bronchitis questionnaire. By identifying participants from the same household it was possible to study varying exposures to tobacco smoke in a subsample of 3960 men and 4037 women and to calculate relative risks for a range of cardiorespiratory variables including mortality.

Four groups, in which the index case was aged 45-64 at the time of the survey, were defined based on the index case and on the cohabitees ever or never having smoked.

(1) Control: the index case had never smoked and lived at the same address as another subject who had never smoked. No one else in the household who attended for screening was a smoker or ex-smoker.

(2) Passive smoking: the index case had never smoked and lived at the same address as a subject who had.

(3) Single smoking: the index case was a smoker or ex-smoker and lived at the same address as a subject who had never smoked. No one else in the household who attended for screening was a smoker or ex-smoker.

(4) Double smoking: the index case was a smoker or ex-smoker who lived at the same address as a subject who was also a smoker or ex-smoker.

If the index cases were ex-smokers they were classified as single smokers or double smokers depending on whether the cohabitees had never smoked or

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Br Med J 1989;299:423-7

Introduction

Though evidence has accumulated about the risk to health of involuntary, or passive, exposure to environmental tobacco smoke, further information is required from cohort studies to confirm these observations. Deleterious effects on the respiratory system of infants and children have been observed^{1,2} as have chronic effects on lung function in adults,^{3,4} but these findings have been criticised on methodological grounds.⁵ An overview of 10 case-control and three cohort studies estimated a relative risk of 1.35 for lung cancer in people passively exposed compared with non-exposed controls.⁶ Three studies have reported increased (though not significant) risks of ischaemic heart disease in non-smokers with partners who smoke.⁷⁻⁹ Problems in interpreting these findings include lack of an objective measure of dose or exposure, failure to adjust for confounding variables, inappropriate methods of statistical analysis, and failure to measure other potentially important variables.¹⁰

This report is based on the Renfrew-Paisley survey, which was carried out in an area with a high incidence

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ever smoked. If the cohabees were ex-smokers the index cases were classified as passive smokers if they had never smoked or as double smokers if they had ever smoked. Thus the controls represent a group whose passive exposure was as low as possible within the constraints of the study design. Results for the two active smoking groups have been included to give some indication of dose-response and provide a perspective for any differences found between the control and passive smoking groups.

A cohabe was defined as a respondent sharing the same household environment and examined at the same time in the survey as the index case. Some households contained cohabees of the same sex. Some of the subjects who were examined were above or below the age range eligible for inclusion in the study. These subjects were not analysed as index cases but information on their smoking behaviour as cohabees was used as the measure of passive exposure for eligible index cases.

Mortality data was obtained from the National Health Service central register and the General Register

Office for Scotland. Incidence of cancer was obtained through the cancer registry system and used to verify that the classification on the death certificate was the same as that received by the registry. Data presented are complete to the end of December 1985, an average follow up of 11.5 years.

Prevalences for respiratory and cardiovascular symptoms were standardised for age and sex using the age and sex distribution of the whole cohort as standard. Similarly, mortality was standardised for age and sex using life tables to estimate survival at 11 years of follow-up.¹⁴

Mean forced expiratory volumes in one second for the four exposure groups were adjusted for age, height, and sex by determining the best fit set of parallel regression models for forced expiratory volume in one second as a linear function of age and height for men and women separately in each group. The mean adjusted forced expiratory volume in one second for each group was then calculated for the average age and height of men and women separately, and a weighted average (corresponding to the proportion of men and women) was computed. Probability values were obtained from the analysis of variance.

Estimates of relative risk and 95% confidence intervals for passive smokers compared with controls were adjusted for age, sex, social class, diastolic blood pressure, serum cholesterol concentration and body mass index (weight (kg)/(height (m))² × 100) using the logistic regression model¹⁵ for cardiorespiratory symptoms and Cox's proportional hazards model for mortality.¹⁶ Levels of significance were derived from the partial likelihood function.¹⁷ The biomedical data processing programs (BMDP) package was used to compute estimates of risk and levels of probability.¹⁸

A supplementary questionnaire in two of the 12 centres in which the survey was carried out asked subjects the extent to which they were exposed to cigarette smoke from any other person in the household, irrespective of whether these people were eligible for or attended the survey, and also in their work environment.

Results

The number of men and women in the four exposure groups is shown in table 1. Passive smokers comprised

TABLE 1—Composition of groups exposed to cigarette smoke

	No (%) of men (index cases)	No (%) of women (index cases)	Total
Controls (neither index case nor cohabe ever smoked)	428 (10.8)	489 (12.1)	917
Passive smoking (only cohabe ever smoked)	243 (6.1)	1295 (32.1)	1538
Single smoking (only index case ever smoked)	1420 (35.9)	331 (8.2)	1751
Double smoking (both index case and cohabe ever smoked)	1869 (47.2)	1922 (47.6)	3791
Total	3960 (100)	4037 (100)	7997

TABLE 2—Social class of men in groups exposed to cigarette smoke. Figures in parentheses are percentages

Social class	Exposure group			
	Controls	Passive smoking	Single smoking	Double smoking
I	23 (5.4)	13 (5.3)	61 (4.3)	78 (4.2)
II	85 (19.9)	37 (15.2)	225 (15.8)	235 (12.6)
III non-manual	63 (14.7)	23 (9.5)	197 (13.9)	204 (10.9)
III manual	157 (36.7)	96 (39.5)	538 (37.9)	771 (41.3)
IV	80 (18.7)	59 (24.3)	315 (22.2)	438 (23.4)
V	17 (4.0)	11 (4.5)	68 (4.8)	122 (6.5)
Insufficient information	3 (0.7)	4 (1.6)	16 (1.1)	21 (1.1)
Total	428 (100)	243 (100)	1420 (100)	1869 (100)

TABLE 3—Smoking habits of cohabees in passive smoking and double smoking groups. Figures are percentages (members)

No of cigarettes smoked per day by cohabe	Index case			
	Men		Women	
	Passive smoking group	Double smoking group	Passive smoking group	Double smoking group
1-14	31.3 (76)	30.0 (561)	15.1 (196)	11.4 (219)
≥15	46.1 (112)	52.7 (985)	41.8 (541)	56.2 (1080)
15-24		42.0 (102)	30.8 (399)	37.1 (713)
≥25		4.1 (10)	11.0 (142)	19.1 (367)
Ex-smoker	22.6 (55)	17.3 (323)	43.1 (558)	32.4 (623)

TABLE 4—Age and sex standardised rates of respiratory and cardiovascular symptoms related to exposure to cigarette smoke. Numbers of index cases with symptoms are given in parentheses

	Exposure group			
	Controls (n=917)	Passive smoking (n=1538)	Single smoking (n=1751)	Double smoking (n=3791)
Respiratory symptoms:				
Infected sputum	2.3 (22)	3.3 (44)	10.5 (189)	10.5 (396)
Persistent sputum	7.8 (72)	9.9 (122)	28.0 (541)	28.7 (1079)
Dyspnoea	10.1 (95)	12.2 (197)	13.4 (229)	16.6 (618)
Hypersecretion	5.3 (48)	6.9 (81)	17.6 (327)	18.3 (681)
Cardiovascular symptoms:				
Angina	4.6 (43)	4.7 (74)	7.7 (165)	9.1 (334)
Major abnormality found on electrocardiogram	1.0 (8)	1.1 (13)	1.4 (31)	1.5 (49)
Mean forced expiratory rate in one second (l):				
Unadjusted	2.32	2.21	2.12	2.09
Adjusted	2.31	2.23	2.12	2.07

TABLE V—Age and sex adjusted mortality per 10 000 per year by category of exposure to cigarette smoke. Figures in parentheses are actual numbers of deaths

	Controls	Passive smoking	Single smoking	Double smoking
All causes	83.1 (99)	97.4 (164)	160.0 (420)	155.6 (734)
Lung cancer	1.6 (2)	5.0 (7)	23.2 (54)	21.4 (93)
Ischaemic heart disease	27.3 (30)	47.7 (54)	61.0 (171)	60.7 (260)
All causes of death related to smoking	60.8 (71)	72.2 (104)	130.4 (362)	129.9 (592)

TABLE VI—Age adjusted prevalence of respiratory and cardiovascular symptoms and age standardised mortality per 10 000 per year for women in control and passive smoking groups. Figures in parentheses are numbers of actual cases

	Controls (n=489)	Passive smokers	
		Low exposure (n=754)	High exposure (n=541)
<i>Prevalence</i>			
Respiratory symptoms:			
Infected sputum	2.1 (10)	2.4 (18)	3.1 (17)
Persistent sputum	6.4 (31)	5.8 (45)	8.6 (46)
Dyspnoea	12.7 (60)	11.2 (84)	16.2 (88)
Hypersecretion	4.1 (19)	3.8 (29)	5.7 (30)
Cardiovascular symptoms:			
Angina	3.6 (17)	4.1 (32)	5.8 (31)
Major abnormality found on electrocardiogram	0.4 (2)	1.1 (8)	0.5 (2)
<i>Mortality</i>			
All causes	58.3 (32)	64.6 (70)	87.8 (54)
Lung cancer	3.2 (1)	2.5 (2)	5.7 (3)
Ischaemic heart disease	6.8 (3)	14.2 (14)	28.0 (16)
All causes of death related to smoking	34.9 (17)	35.2 (39)	47.3 (30)

6.1% (243/3960) of men and 32.1% (1295/4037) of women. Of the cohabiters, 91.6% (7325) were of the opposite sex. The composition of the groups by social class is shown in table II.

The extent of passive exposure experienced by passive smokers in relation to subjects in the double smoking group is shown in table III. In all, 46.1% (112) men and 41.8% (541) women in the passive smoking group lived in households where the cohabitee was smoking 15 or more cigarettes a day. This compared with 52.7% (985) men and 56.2% (1080) women in the double smoking group. Ex-smokers were more common in households in which the index case had never smoked.

The prevalence of signs and symptoms for the four exposure groups is shown in table IV. For each of the four respiratory measures (infected sputum, persistent sputum, dyspnoea, and hypersecretion) the rates in the control group were lower than those in the passive smoking group and considerably lower than in the single and double smoking groups. The rates for angina and major abnormalities found on electrocardiography were similar in the control and passive smoking groups and lower than in the active smoking groups.

Mean forced expiratory volumes in one second adjusted for sex, age, and height were significantly higher ($p < 0.01$) in controls than in those passively

exposed to cigarette smoke and were significantly higher than among active smokers.

Mortality adjusted for age and sex in the four groups is presented in table V. Total mortality was higher among passive smokers than controls. This was reflected in the category of all causes of death related to smoking and was highest for ischaemic heart disease. Lung cancer mortality was higher among passive smokers than controls, but the number of deaths involved was small.

The supplementary questionnaire on exposure to cigarette smoke at home and work allowed a check to be made of the smoking habits of other household members who were not part of the survey. A regular smoker living in the same household was reported by 5% (2/44) of controls compared with 69% (27/39) of passive smokers. Of women, 21% (13/62) of controls lived in households with a regular smoker compared with 63% (125/197) of passive smokers.

Women reported that most of their passive exposure was at home rather than at work, which suggested that they were the appropriate group in which to examine whether there was a dose-response relation. A high exposure passive smoking group was therefore defined as women whose cohabitee was smoking 15 or more cigarettes daily, and the remaining female passive smokers were defined as a low exposure group. Table VI presents the age standardised rates for respiratory and cardiovascular symptoms and mortality for the control and the low and high exposure passive smoking groups. For each of the four respiratory symptoms the highly exposed passive smokers had rates that were higher than those in passive smokers whose exposure was low and those in the controls. There were no consistent differences between the low passive exposure group and the controls. A similar pattern was found for angina but not for major abnormalities detected by electrocardiography.

The adjusted forced expiratory volume at one second was significantly lower in passive smokers with high exposure compared with those with low exposure (mean 1.831 ± 1.891 ; $p < 0.05$). No significant difference was found between passive smokers with low exposure and controls (1.891 ± 1.881). Age adjusted mortality was increased for the passive smokers with high exposure compared with low and with controls for all cause mortality, all cause mortality related to smoking, ischaemic heart disease, and lung cancer.

Table VII shows the adjusted relative risks for passive and active smokers compared with controls. For each variable the relative risk associated with passive smoking was > 1.0 . The confidence interval included 1.0 except for ischaemic heart disease, for which the estimate of risk was significantly different from unity ($p = 0.008$).

Table VIII shows the relative risks for double smokers compared with single smokers after additional adjustment for quantity smoked. Dyspnoea was signi-

TABLE VII—Relative risks associated with passive smoking adjusted for age, sex, and social class and for cardiovascular variables, diastolic blood pressure, serum cholesterol concentration, and body mass index

	Relative risk (passive smokers compared with controls)	95% Confidence interval	p Value	Relative risk (active smokers compared with controls)
Respiratory symptoms:				
Infected sputum	1.34	0.76 to 2.36	0.3	4.53
Persistent sputum	1.19	0.85 to 1.67	0.3	4.49
Dyspnoea	1.49	0.82 to 1.45	0.5	1.60
Hypersecretion	1.21	0.81 to 1.82	0.3	3.77
Cardiovascular symptoms:				
Angina	1.11	0.73 to 1.70	0.6	1.09
Major abnormalities found on electrocardiogram	1.27	0.46 to 3.35	0.6	1.51
Mortality:				
All causes	1.27	0.95 to 1.70	0.10	2.07
All causes of death related to smoking	1.30	0.91 to 1.85	0.15	2.33
Ischaemic heart disease	2.01	1.21 to 3.35	0.008	2.27
Lung cancer	2.41	0.45 to 12.83	0.3	10.64

TABLE VIII—Relative risks in double smokers compared with single smokers, adjusted for age, sex, amount smoked, and social class and for cardiovascular variables, diastolic blood pressure, serum cholesterol concentration, and body mass index

	Relative risk	95% Confidence interval	p Value
Respiratory symptoms:			
Infected sputum	0.96	0.79 to 1.16	0.65
Persistent sputum	1.06	0.92 to 1.21	0.45
Dyspnoea	1.25	1.05 to 1.49	0.02
Hypersecretion	1.02	0.87 to 1.20	0.75
Cardiovascular symptoms:			
Angina	1.17	0.95 to 1.44	0.15
Major abnormalities found on electrocardiogram	1.11	0.68 to 1.79	0.65
Mortality:			
All causes	1.01	0.87 to 1.18	0.9
All causes of death related to smoking	0.99	0.84 to 1.16	0.9
Ischaemic heart disease	0.89	0.72 to 1.11	0.3
Lung cancer	1.13	0.79 to 1.63	0.5

significantly more common among double smokers ($p=0.02$), and though none of the other variables was significant, six had risks >1.0 .

Discussion

Whether inhaling other people's tobacco smoke is a risk factor for lung cancer and other diseases related to smoking is now under serious scientific consideration. Studies of the concentrations of cotinine in the urine and saliva of passive smokers suggest that the dose received may be equivalent to smoking up to three cigarettes a day.¹⁰ Though sidestream smoke contains different proportions of chemical constituents than does mainstream smoke and the same dose received passively might not translate directly to the same risk as in active smokers, the risks expected for passive smokers will probably be of a similar magnitude to those found in active smokers of up to three cigarettes daily; consequently, only very large studies will have sufficient power to detect such risks. A meta-analysis is currently the only way to establish precise estimates of risk, and it is essential that all studies are included.

This paper updates a previous publication¹¹ with mortality now extended to an average follow up time of 11.5 years and the control and passive smoking groups redefined to exclude those who smoked only pipes or cigars and those who smoked cigarettes irregularly. The original questionnaire in its coded form did not distinguish pipe and cigar smokers and those who smoked fewer than five cigarettes a day from non-smokers. Written information on the questionnaires allowed this to be clarified, and these additional data were added to the computer files.

The sample size in this study does not provide sufficient statistical power to detect risks of the magnitude expected. Thus the lack of significance should not be the sole criterion of whether a genuine effect may be present. Several findings should be borne in mind when interpreting these results. Firstly, for each of the 10 measures examined, from respiratory symptoms to causes of mortality, the relative risk was consistently larger than unity. This remained so after adjusting for intervening risk factors such as age, sex, social class, blood pressure, cholesterol concentration, and body mass index. Secondly, the one measure for which sufficient statistical power was available—that is, forced expiratory volume in one second—gave a significant result. Thirdly, when a group of passive smokers with high exposure was defined there was an increase in the dose-response relation for nine of the 10 variables. Fourthly, in comparison with the relative risks found for the two active smoking groups, each increased risk was biologically plausible, with the possible exception of that for ischaemic heart disease.

The findings for respiratory symptoms are similar to those of other studies: a decreased forced expiratory volume in one second in passive smokers has been

found previously,¹² and the risks for lung cancer are consistent with those in the overview by Wald *et al.*¹³ Few data relate passive smoking to cardiovascular disease, but a relative risk as high as 2.2 for mortality from ischaemic heart disease in passive smokers has been quoted.¹⁴ Our risk of 2.0 seems large in comparison with that found for active smokers, and the possibility that chance has inflated this risk cannot be excluded, but as the lower 95% confidence limit for the relative risk is greater than one it would appear that chance alone is not responsible for the excess.

When investigating risks close to unity it is important to consider the effect of potential biases. Biases may operate at the time data are collected. Between 1972 and 1976, however, passive smoking was not an issue. Subjects reported their own smoking habits and no self reporting of passive exposure was undertaken. It was not until 1983 that subjects within the same household were linked, and this was carried out without any reference to the measures of outcome examined subsequently.

There is no direct measure available to prove that the passive smokers received a higher environmental dose of tobacco smoke than the controls, but in the supplementary questionnaire that covered the smoking habits of household members irrespective of whether they attended the original survey only 5% of controls said that there was a current smoker in the household, compared with 63% of passive smokers. Greater exposure to tobacco smoke at work supported the idea that passive smokers were more likely than controls to be in contact with environmental tobacco smoke outside the home. This was measured by Wald and Ritchie,¹⁵ who showed that non-smoking husbands of smoking wives had higher urinary cotinine concentrations than non-smoking husbands of non-smoking wives. Our definition of categories of exposure is comparable with that of other studies and would seem to identify groups with different mean levels of passive exposure. The high level of heavy smoking in our cohort¹¹ might also indicate that this difference is greater than that found in other studies.

The problem of smokers deliberately classifying themselves as non-smokers¹⁶ is a far less serious bias in cohort studies than in case-control studies, because at the interview stage there is no indication which subjects will subsequently die. The likelihood of differential misclassification rates—that is, higher in the passive smoking than in the control group—is debatable as this implies that someone in the double smoking group is more likely to pretend to be a non-smoker than someone in the single smoking group. When the cohabitee is a smoker the reverse may be more likely to be true.

It has been suggested that non-smokers who marry smokers may be different from non-smokers who marry non-smokers.¹⁷ A higher proportion of passive smokers were in social classes III manual, IV, and V, but no differences were found for other possible risk factors such as occupation, raised blood pressure, cholesterol concentration, or body mass index. In any case the final analysis, which estimated the relative risks, adjusted for each of these factors.

The effect of passive smoking on those who already smoke is far harder to isolate. The dose received by active smokers from smoking ranges widely,¹⁸ and adding a small extra component due to passive exposure may not lead to much of a difference in mean doses for double smokers compared with single smokers. Hence, the increased risk for double smokers relative to single smokers may be substantially less than that for passive smokers relative to controls. Thus the statistical power of a single study is an important consideration and in the absence of other published data on this aspect it is difficult to interpret our results

for the effects of passive smoking on smokers. Therefore the main emphasis of this paper is an estimation of the risks of passive smoking in lifelong non-smokers; data are presented for the active smoking groups to provide an estimate of dose-response.

Our results are based on a general population cohort study carried out in an area with a high level of diseases related to smoking. A consistent increase in risk was observed in passive smokers for each of the 10 variables measured covering respiratory symptoms, forced expiratory volume in one second, cardiovascular symptoms, and subsequent mortality, including lung cancer and ischaemic heart disease. A dose-response relation was seen, and the risks were biologically plausible in relation to the size of the risks found for the active smokers. These three factors taken together increase our concern that exposure to other people's tobacco smoke cannot be regarded as a safe involuntary practice.

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Carbohydrate deficient transferrin: a marker for alcohol abuse

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Abstract

Objective—To assess the value of serum carbohydrate deficient transferrin as detected by isoelectric focusing on agarose as an indicator of alcohol abuse.

Design—Coded analysis of serum samples taken from patients with carefully defined alcohol intake both with and without liver disease. Comparison of carbohydrate deficient transferrin with standard laboratory tests for alcohol abuse.

Setting—A teaching hospital unit with an interest in general medicine and liver disease.

Patients—22 "Self confessed" alcoholics admitting to a daily alcohol intake of at least 80 g for a minimum of three weeks; 15 of the 22 self confessed alcoholics admitted to hospital for alcohol withdrawal; 68 patients with alcoholic liver disease confirmed by biopsy attending outpatient clinics and claiming to be drinking less than 50 g alcohol daily; 47 patients with non-alcoholic liver disorders confirmed by biopsy; and 38 patients with disorders other than of the liver and no evidence of excessive alcohol consumption.

Intervention—Serial studies performed on the 15 patients undergoing alcohol withdrawal in hospital.

Main outcome measure—Determination of relative value of techniques for detecting alcohol abuse.

Results—Carbohydrate deficient transferrin was detected in 19 of the 22 (86%) self confessed alcohol abusers, none of the 47 patients with non-alcoholic

liver disease, and one of the 38 (3%) controls. Withdrawal of alcohol led to the disappearance of carbohydrate deficient transferrin at a variable rate, though in some subjects it remained detectable for up to 15 days. Carbohydrate deficient transferrin was considerably superior to the currently available conventional markers for alcohol abuse.

Conclusion—As the technique is fairly simple, sensitive, and inexpensive we suggest that it may be valuable in detecting alcohol abuse.

Introduction

The medical and social consequences of alcohol abuse are major problems throughout the world. Although many people readily acknowledge the extent of their alcohol consumption, others attempt to conceal it, and we lack reliable objective means of identifying surreptitious alcohol consumption. Currently available laboratory markers have considerable limitations, being insensitive, non-specific, or dependent on liver damage. The mean corpuscular volume rises in patients with thyroid disease, folic acid deficiency, and liver disease,¹ whereas serum γ -glutamyltransferase activity is affected by drugs that induce microsomal enzymes as well as rising in all forms of obstructive liver damage.² Serum aspartate aminotransferase activity is more commonly raised in alcoholics than alanine aminotransferase activity is, and whereas a ratio of aspartate to alanine aminotransferase activity of greater than 2:1 is strongly suggestive of alcoholic liver disease³ this is of little value in subjects in whom the

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adrenergic casualty department, where further delays would take place and possibly further errors by inexperienced junior staff. Unfortunately, the message of the British Heart Foundation report is deeply ambivalent, doubtless reflecting a "dissensus" in the group. The overall result, however, will be to discourage general practitioners from participating fully and exploiting the major benefits that thrombolytic treatment can confer. Rather than "contracting out," as the report suggests, I hope that general practitioners will insist on local schemes to bolster their confidence in the full early management of myocardial infarction.

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of the above automated methods, and the rather glib dismissal of necessary technician time shows a lack of understanding for the problems of laboratories that will be asked to perform these investigations on a day to day basis, given the current volume of requests for markers of alcohol abuse.

Chemical pathology departments that seek to sell this "fairly simple, sensitive, and inexpensive" technique to their managers and clinicians as an alternative to cheaper current tests (albeit with known limitations) may thus be hoist with their own petard.

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Passive smoking and cardiorespiratory health in Scotland

SIR.—Mr David J Hole and colleagues, when discussing results from their prospective study, state that studies of cotinine in passive smokers suggest that the dose received may be "equivalent to smoking up to three cigarettes a day." To support this misleading statement they cite a solitary study in Japan¹ in which urinary cotinine concentrations in non-smokers averaged 8% of those in smokers. This contrasts sharply with evidence from Western populations,² which indicates that average cotinine concentrations in non-smokers exposed to environmental tobacco smoke are about 0.7% of those in smokers. Blott and Fraumeni speculated that Japanese people might have especially heavy exposure to environmental tobacco smoke.³ Other studies in Japan⁴ (and abstracts presented by S Umemura and colleagues⁵ and E Higashi and colleagues, international conference on indoor air quality, Tokyo, 1987) have, however, sustained earlier suspicions⁶ that the methodology used in the original study⁷ was faulty. When estimating passive exposure relative to that from active smoking nicotine based indices are of dubious value, partly because nicotine in environmental tobacco smoke, unlike that in mainstream smoke, is largely in the vapour phase and need not be absorbed by the lungs.⁸ Based on measurements of retained particulate matter, exposure to environmental tobacco smoke averages at about 0.05% of the exposure of a person who smokes 20 cigarettes each day—that is, 0.01 cigarettes a day.

That such minute doses should elicit observable health effects is surprising, and epidemiological studies that report associations with exposure to environmental tobacco smoke have been critically examined for possible bias. One important bias arises because some smokers deny present or past smoking. Mr Hole and colleagues refer to one of my papers,⁹ but unfortunately have totally misunderstood how such bias arises. They state that differential rates of misclassification imply that someone in their "double smoking group" has to be "more likely to pretend to be a non-smoker than

someone in the single smoking group." This is untrue because it overlooks the fact that smokers tend to cohabit with smokers.

The table shows how differential misclassification can arise, assuming 2% of the index subjects had denied smoking. The higher proportion of smokers (15.6%) in the observed passive smoking group compared with the observed control group (6.8%) would cause substantial bias for an end point strongly related to active smoking. Thus if risk were increased 20 times in smokers, and not by exposure to environmental tobacco smoke, the relative risks observed would be 6.90 for active smoking and 1.74 for passive smoking, not 2.0 and 1 respectively. Many studies have shown higher rates of denial of smoking than assumed in the table,¹⁰ so this source of bias is evidently important. It can explain the many positive associations reported in the Scottish study,¹¹ most of which were not statistically significant.

The results for lung cancer from the Scottish study were based on only nine deaths among self reported non-smokers. This contrasts with over 2000 deaths in other published studies. Clearly, the new data contribute little to the overall picture. Evidence on environmental tobacco smoke and heart disease has previously been reviewed and considered inconclusive.¹² Although the Scottish study reported more deaths from heart disease than from lung cancer, it should not materially affect this view.

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Donating drugs to the Third World

SIR.—As director of Intercare, the organisation approved by the BMA Board of Science and Education for promoting the salvaging of suitable medical supplies for use in the Third World, I am happy to answer the criticisms expressed by Dr Frances Griffiths.¹

Marker for alcohol abuse

SIR.—The prospect of a more reliable marker for alcoholism as described by Mr A Kapur and colleagues is most welcome. Unfortunately, however, their last paragraph states that "the cost of the test compares favourably with that of other standard laboratory investigations." The given method does not specify the reagents closely enough for the costs of consumables to be worked out, but I challenge Mr Kapur and colleagues to produce a result for 22p per specimen (the current cost of consumables for a γ -glutamyltransferase estimation in this department). A full blood count (including mean corpuscular volume) performed by our haematology department represents even better value at 11p for consumables. The isolation and identification of carbohydrate deficient transferrin is patently more labour intensive than either

Differential misclassification caused by 2% of index subjects denying smoking regardless of cohabitant's smoking habits

Exposure group*	Smoking state of index subject	Smoking state of cohabitee	"True" distribution	Effects of denial	Observed distribution†	Percentage who have smoked‡
Controls	Non-smoker	Non-smoker	399	-29	428	6.8
Passive smokers	Non-smoker	Smoker	203	+38	241	15.6
Single smokers	Smoker	Non-smoker	1449	-29	1420	
Double smokers	Smoker	Smoker	1937	+38	1975	

*As defined by Hole et al.

†Data from table 1 of Hole et al.

‡Among the observed population.

council of the Royal College of General Practitioners and the General Medical Services Committee (Wales).

In overall terms our deputation feared that the general principles of the referral system were compromised, access to specialist psychiatric services was ill defined, and the declared role of the mental health team in primary care could lead only to fragmentation and confusion. Furthermore, the contractual obligations of the general practitioner were totally bypassed.

The deputation received a sympathetic hearing, and it was with great disappointment that we read the final paper, *Mental Health Services, a Strategy for Wales*, issued in June 1989. Little has changed from that set out in the consultation document, and we are convinced that if the recommendations of this paper are implemented the task of treating psychiatric disorder in Wales is likely to be muddled and expensive.

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Rape and subsequent seroconversion to HIV

SIR.—The paper by Dr S Murphy and colleagues highlights the potential risks and worries for women who have been sexually assaulted during the current phase of the HIV epidemic.¹ If we assume that such assailants are heterosexual men the overall risk of transmission is likely to be small in view of the present low carriage rate for the virus among this group in Britain.² In addition, vaginal intercourse is possibly a less likely mode of transmission than anal intercourse.³ The situation for male victims of sexual assault may, however, be different.

Male "rape" as a legal term does not exist in the United Kingdom, as rape specifies forcible vaginal penetration. Furthermore, male sexual assault is not recognised as a distinct entity within the 1976 Sexual Offences (Amendment) Act.⁴ This may well have consequences for the number of cases reported and for public awareness of such events.⁵ Documented cases of sexual assault of men by women have been reported,⁶ but it is generally thought that men are more commonly assaulted by other men.

In the United States it has been estimated that only 10-20% of all sexual assaults are ever reported.⁷ In addition, there is some evidence to suggest that male victims are more reluctant to come forward than their female counterparts, possibly related to the fear of being labelled as homosexual⁸ or to society's concept that a "real man" cannot be raped.⁹

Partly as a consequence of its legal non-existence there are no reliable figures of the frequency and nature of male sexual assault in Britain. The only organisation providing care for victims of male sexual assault in Britain at present is "Survivors," a service run by volunteers to which various government and charitable agencies refer their clients. The service provides a telephone help line (currently answering just over 100 inquiries a month) together with counselling and support. No studies to date have assessed the risk of sexually acquired infection in male victims of assault,¹⁰ but of 512 victims known to Survivors in 1988, 24 of 73 who sought medical advice were diagnosed as having a sexually transmitted disease presumed to be consequent on their assault. Data on HIV seroconversion are not available, but 148 of the 512 victims reported skin or mucosal bleeding, and 278

expressed concern about the possibility of transmission of HIV. In 92 of the cases the assailant deliberately threatened the victim with the possibility of contracting HIV infection as a consequence of the assault.

It has been suggested that between 50%¹¹ and 82%¹² of assailants of male victims are either homosexual or bisexual. The assailants are therefore in relatively higher risk groups for HIV infection than heterosexual assailants of women. Furthermore, anal penetration, bloody non-genital violence, and multiple assailants are more likely when the victim is male.¹³

Rape treatment centres have been set up primarily for female victims and may lack the skills to deal with men. We believe that an increased level of awareness of male sexual assault is needed among the general public and especially by health care professionals to encourage victims to come forward. Only when this happens can the scale of the problem be fully grasped and appropriate treatment provided.

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Passive smoking and cardiorespiratory health in Scotland

SIR.—Mr Peter N Lee¹ implies that our observation of increased risk for four respiratory symptoms and two cardiovascular symptoms, mortality from lung cancer, mortality from ischaemic heart disease, all causes of death related to smoking, and mortality from all causes in passive smokers compared with controls² can be explained by bias—that of smokers declaring themselves to be lifelong non-smokers. He cites (presumably) lung cancer, for which if, as he supposes, no increased risk is associated with exposure to environmental tobacco smoke and the "true" risk is increased 20 times in active smokers,

2% of smokers denying smoking would result in observed relative risks of 1.74 for passive smokers and 6.90 for active smokers. This is illustrated in his table, using the distribution of subjects in the smoking groups defined in our study. But why does he use only men and ignore women when our analysis and results were based on both sexes and women comprised 84.2% of our passive smokers? If he had included women 5.0% of passive smokers and 3.9% of controls would have smoked (table 1)—quite different from the figures of 15.6% and 6.8% respectively presented in his table. Our figures in turn produce an observed relative risk of 1.12 for passive smoking (substantially less than the 1.74 he quotes by selecting only men) and considerably less than our study finding of 2.41 for lung cancer among passive smokers. Clearly, misclassification owing to the 2% rate of denial of smoking he suggests does not explain our finding.

In addition, higher rates of denial of smoking do not produce sufficient bias to explain our risk for lung cancer. Table 2 presents the effect on the basis of a "true" relative risk of 20 for active smoking and 1 for passive smoking and of rates of denial varying from 1% to 10%. Two facts emerge: firstly, the bias in the relative risk for passive smokers does not increase linearly as the rate of denial increases, it flattens considerably; secondly, the observed relative risk for active smokers diminishes rapidly as the rate of denial increases.

TABLE 2—Relative risks for passive and active smoking for varying rates of smoking

Rate of denial (%)	Observed relative risk	
	Passive smokers	Active smokers
1	1.07	13.95
2	1.12	10.67
3	1.15	8.61
4	1.18	7.17
5	1.19	6.14
6	1.20	5.35
7	1.21	4.73
8	1.22	4.23
9	1.23	3.82
10	1.23	3.47

This is important, as by comparing the observed relative risk for active smokers from the table with the relative risk found in the study an upper bound can be defined for the rate of denial. The study relative risk for active smokers compared with lifelong non-smokers is 5.85. This would be incompatible with rates of denial greater than 5%. Therefore, the largest relative risk to be expected among passive smokers due to this form of bias when the "true" risk is unity is 1.20. A relative risk of 2.41 was found in our study.

Again, the same approach applied to ischaemic heart disease assuming a "true" relative risk of 3 for active smokers and 1 for passive smokers and a rate of denial of smoking of 5% produces an observed relative risk of 1.05 for passive smokers and 2.42 for active smokers. Thus if the relative risk for active smokers is considerably less than 20, as in all the conditions we considered other than lung cancer, the effect of misclassification is to produce only small biases in the relative risk for passive smokers. Our risks for each of the respiratory symptoms, cardiovascular symptoms, and cate-

TABLE 1—Differential misclassification caused by 2% of index subjects denying smoking regardless of cohabitee's smoking habits

Exposure group*	Observed distribution†	"True" distribution	Effects of denial	Percentage who have smoked
Controls	917	881	+36	3.9
Passive smokers	1538	1461	+77	5.0
Single smokers	1751	1787	-36	
Double smokers	3791	3868	-77	

*As defined by Hole et al.¹ †Data from table 1 of Hole et al.²

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gories of mortality quoted are well in excess of that produced by the form of bias suggested. Also, as control subjects experience some level of environmental tobacco smoke¹ our estimates of risk could be conservative.

Mr Lee misunderstands our use of urinary cotinine concentrations in passive smokers. We were using published data to establish whether our study had sufficient statistical power to detect the size of risk that might be expected among passive smokers. If Mr Lee is correct and urinary cotinine concentrations are equivalent to a lower dose than assumed then our decision not to rely solely on statistical significance as evidence of a genuine effect was definitely correct. Ours was a cohort study of a general population and was not subject to the biases associated with a case-control design. In addition, subjects reported their own smoking histories, and environmental exposure was based on record linkage of cohabitantes, thereby avoiding the need to rely on self reporting of passive exposure.

Our observations on lung cancer may be based on only nine deaths but are consistent with the result of a meta-analysis² combining 13 separate studies, which concluded that breathing other people's tobacco smoke causes lung cancer. The importance of our study lies in the estimates of risk for ischaemic heart disease (based on 84 deaths), all causes of death related to smoking (175 deaths), mortality from all causes (263 deaths), respiratory symptoms (292 cases), and cardiovascular symptoms (117 cases). The consistent increase in risks for such a wide variety of health outcomes from an unbiased prospective cohort study together with a dose-response relation in passive smokers strongly suggests that there is now a case to be answered against passive smoking that extends beyond the causation of lung cancer.

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Referrals from general practice to hospital outpatient departments

STR.—One aspect highlighted in the report by Drs John Emmanuel and Nigel Walker¹ is treatment of skin disorders in general practice. Proposals in the white paper are likely to encourage more minor surgery to be undertaken by general practitioners. This may be more cost effective (although our own experience indicates that this may not necessarily be so), but skin surgery should be undertaken in general practice only if the diagnosis is certain—otherwise referrals may be increased rather than decreased as intended. We report two problems that resulted from inappropriate skin surgery in general practice.

A 49 year old woman had a pigmented lesion removed by curettage and cautery from her lower leg by her general practitioner. Histology showed malignant melanoma, but it was impossible to ascertain the depth of the tumour on the basis of the inadequately thin curettage specimen. The patient then had a wide excision and graft, but it is

possible that she would not have required an extensive operation because narrow excision margins can sometimes be adequate for very thin melanomas.

In another patient, a 46 year old woman, a slightly raised nodule on the leg was treated by curettage and cautery by her general practitioner. Histology showed invasive squamous cell carcinoma and the patient was referred for further advice. Because it was difficult to know the adequacy of the initial treatment the patient was committed to prolonged follow up to exclude recurrence of the lesion.

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Provision of services

STR.—It seems to be the custom that when a specialist advisory committee pronounces on how services should be provided this is accepted; but there are occasions when someone needs to stand up and say "You are wrong."

The North West Thames ear, nose, and throat regional advisory subcommittee says that inpatient ear, nose, and throat services should be provided only in subregional specialist centres and not in the smaller district general hospitals. I have been the anaesthetist for three to four ear, nose, and throat lists per week for over 20 years and know that most of these operations are everyday bread and butter surgery and that over half are on children. Indeed the commonest paediatric operations are ear, nose, and throat—tonsils, glue ears, etc. These services have always been available at the local hospital and to say they should all go to subregional centres is tantamount to saying all hernias and ingrowing toenails should go to specialised units. Not only does this deprive patients of what I would call a core service but it has profound knock on effects on most other services in the district general hospital through the possible loss of recognition of anaesthetic jobs. Before someone brings out the old chestnut of "Make rotations" I will answer "Just you try to."

We are facing this situation in North West Hertfordshire District, where the loss of inpatient ear, nose, and throat services will disadvantage our patients and could cause havoc with the hospital services as a whole. I am afraid that this may be only the beginning of specialist groups building their own little empires without regard to the patients and hospitals from whom they withdraw their services.

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Psychiatric illness among the homeless

STR.—Dr Max Marshall describes a high proportion of residents of Oxford hostels for the homeless as being "long term psychiatric patients" and implies that they are deinstitutionalised long stay patients. Our findings, however, suggest that hostel residents with psychiatric disabilities may have had numerous yet relatively brief hospital admissions and include those sometimes referred to as "revolving door" patients.

We are currently evaluating a psychiatric liaison

service to residents of a direct access hostel for homeless women in central London. Of 33 women seen to date, 26 are known to have had at least one previous psychiatric admission, but only four have spent periods of more than one year continuously as inpatients. We believe the current emphasis on deinstitutionalised long stay patients is misplaced: it is the needs of those with chronic, severe psychiatric disabilities in the community and the revolving door patients that are not being addressed. Deferring the closure of psychiatric hospitals will have little impact on this large group of people. The Department of Health has stated that the forthcoming white paper on community care will contain plans to prevent the unplanned discharge of long stay patients into the community. These safeguards will be of no value to most severely disabled psychiatric patients in the community.

Dr Marshall's findings and our own data both show high levels of unmet need and are in keeping with most surveys of people with psychiatric disorders in the community. These findings clearly indicate inadequate provision of care, but they should not be used as evidence of the ineffectiveness of deinstitutionalisation programmes or properly planned and funded community services. The few controlled studies of selected patients discharged within carefully planned community programmes¹ show that long term psychiatric patients (whether or not they have had long stay psychiatric admissions) can be maintained outside hospital without the deterioration in symptoms, poor psychosocial functioning, and readmissions that are all too commonly found in the surveys. Perhaps more importantly, the controlled studies in which patients' wishes and satisfaction have been recorded clearly show that they prefer to be treated in the community.

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Safety of Picolax in inflammatory bowel disease

STR.—In view of the suggestion of Dr A J G McDonagh and colleagues that further evaluation of Picolax is merited¹ we would like to report our own experience with this preparation in a large cohort of children undergoing fiberoptic colonoscopy at St Bartholomew's Hospital. Between 1982 and 1988 we performed 534 colonoscopies on 412 children attending this hospital and, with few exceptions, Picolax was used routinely to prepare the colon before endoscopy. This included the 287 procedures performed on children with chronic inflammatory bowel disease (163 with Crohn's disease, 101 with ulcerative colitis, 23 with indeterminate colitis) that was either known to pre-exist or suspected and confirmed at the time of endoscopy. We found the preparation to be successful for cleansing the bowel and free of major complications.

Based on our experience we have developed the following regimen for preparing the colon before endoscopy in children. The child is given only fluids for 24 hours before the procedure and is given two doses of Picolax, one about 15 hours before endoscopy and the other three hours before. The dose is age dependent: children over 6 years

unlikely to be of value and often causes unnecessary anxiety. Nutrition is better assessed using skinfold calipers (which are also cheaper and more portable than weighing scales) to measure directly the thickness of subcutaneous fat.¹

Accurate height measurement (supine length in infants under 2 years) is a sensitive guide to child health. Growth velocity (calculated from repeated measurements of height at intervals) represents the current dynamics of growth much better than a single measurement, which reflects previous growth. Regular, accurate measurement of children can identify those who would benefit from medical, social or educational intervention.⁴

Many height measurements in hospital and the community are inaccurate and misleading because of careless techniques and inadequate apparatus. Suitably accurate, cheap, and portable apparatus is now widely available for use in primary care, and measuring techniques eliminating postural drops and positional errors are readily learnt by motivated staff. Supine length in children under 2 years can generally be measured accurately with the help of an assistant.

Collected accurate growth (height) data in children have important benefits beyond those to the individual—as an index of the health of a population or a subgroup (for example, ethnic group or social class). British data are not available and would be valuable.

Many who care for children lack the skill to measure them accurately, plot measurements on a growth chart, and interpret the data obtained. As the report states, such understanding is essential for growth monitoring. More must be done to make those who look after children aware of the need to measure height accurately and regularly throughout childhood and to train them to do so.

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SIR.—*Health For All Children*, discussed by Dr Leon Poinat and Dr D M B Hall, is the result of a working party set up by groups representing paediatricians and general practitioners, neither of whom is disinterested. The British Paediatric Association suggested some years ago that senior clinical medical officers in the child health service should be replaced by "community paediatricians" who would work part time as paediatricians in the hospital and would take part in the on call duty roster. Similarly, much of the interest in taking over child health surveillance by general practitioners has been tied to the proposal that extra payments would be made for such a service. Practitioners who have a real interest in this work provide such a service already for patients on their lists. Bodies that actually represent the medical officers who work in the child health service were not invited to join the working party.

Child health surveillance requires a different outlook from clinical medicine, and it is not easy for clinicians whose whole training has been directed to the diagnosis and treatment of disease to stop thinking in such terms and abandon their prescription pads. Clinicians are not the most appropriate group to advise on a child health service that they do not fully understand.

Developmental assessment and child health surveillance were pioneered by the former child health group of the Society of Medical Officers of

Health, which started running full time training courses of six weeks' duration for doctors some 30 years ago. In the early 1970s when the Faculty of Community Medicine was formed community health doctors were not eligible for membership. Fortunately, a number of medical schools started to run training courses in child development to fill the need that resulted. There was, however, no organisation or body monitoring the standard or content of those courses, which varied widely.

Following the formation of the Faculty of Community Medicine residual members of the Society of Community Medicine sought to promote the interests of community health as well as community medicine. In 1988 the society (which has since changed its name to the Society of Public Health) was instrumental in establishing a new Faculty of Community Health to produce syllabuses, set standards, and appoint examiners. In future, membership of the Faculty of Community Health should be evidence of eligibility for posts as senior clinical medical officer or as consultant in community child health—more appropriate to the needs of the clients and of the child health and education services than "community paediatricians."

We hope that this faculty will provide training for general practitioners in child health surveillance and that appropriate diplomas will be established.

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Passive smoking and cardiorespiratory health in Scotland

SIR.—In an earlier letter¹ I claimed that misclassification of active smoking state can explain the fact that Mr David J Hole and his colleagues² found weak positive associations between passive smoking and a number of indicators of cardiorespiratory health in the Scottish prospective study. In their reply Mr Hole and colleagues presented calculations to justify their view that the effect of misclassification is to produce "only small biases in the relative risk for passive smokers," with the reported relative risk "well in excess" of that produced by this form of bias.³ Unfortunately, these calculations are grossly in error and therefore highly misleading.

The error lies in basing calculations on results for men and women combined without adjustment for sex. Table I of the original paper² shows a clear

TABLE I—"Observed" relative risks for passive smoking for varying denial rates of smoking*

Rate of denial (%)	Relative risks for passive smoking			
	Sexes combined		Adjusted†	
	Men	Women	Adjusted†	Unadjusted‡
2	1.74	1.25	1.40	1.12
4	1.95	1.42	1.58	1.18
6	2.06	1.54	1.70	1.20
8	2.11	1.63	1.78	1.22
10	2.15	1.70	1.84	1.23

* Assuming "true" relative risks of 1.10 for passive smoking and 20.0 for active smoking.

† Adjusted for sex using weights $N_1/N_2(N_1+N_2)$, where N_1 and N_2 are the observed numbers of exposed and unexposed subjects. This is a conservative approximation to the true adjusted figure, which cannot be calculated precisely from the data provided by Hole *et al.*

‡ As given by Hole *et al.*

association between the smoking habits of the index case and the cohabitee, with the concordance (cross product) ratio being 2.32 for men and 2.19 for women. An appropriate estimate of the concordance ratio for the sexes combined with sex adjustment by the Mantel-Haenszel procedure⁴ is 2.25. If, inappropriately, the concordance ratio is calculated from the pooled data, a much lower figure of 1.29 is obtained, and this masks most of the true association. This is important because it can readily be shown that the concordance ratio provides the upper limit to the extent of the observed relative risk from passive smoking due to misclassification of smoking habit (assuming a true relative risk of 1.0). Table I shows that when correctly calculated the observed relative risk can far exceed the value of 1.20 stated by Mr Hole and his colleagues to be "the largest risk to be among passive smokers due to this form of bias."

The question arises as to the extent that this source of bias can explain all the reported relative risks for active and passive smoking seen in the Scottish study. Table II gives some insight into this question, showing "observed" and "true" relative risks assuming a 4% denial of smoking, a figure consistent with data from many studies of the issue.⁵ Comparing the "observed" relative risks of active and passive smoking with those given in

TABLE II—"Observed" relative risks for passive and active smoking for varying "true" relative risks for active smoking*

	"True" relative risks		"Observed" relative risks	
	Passive smokers	Active smokers	Passive smokers	Active smokers
1	30	1.70	9.17	1.81
1	20	1.58	7.88	1.62
1	10	1.39	5.62	1.33
1	5	1.23	3.63	1.13
1	3	1.13	2.50	1.07
1	2	1.07	1.81	1.01

* Assuming 4% of smokers deny smoking. Results are for sexes combined adjusted for sex as in table I.

table VII of the original paper² shows that there is no problem whatsoever in reconciling the data with the bias hypothesis for most of the cardiorespiratory endpoints. For example, relative risks of 3.77 (active) and 1.21 (passive) for hypersecretion are both very close to the values given in table II for a "true" active risk of 5 (1.23 and 3.63, respectively).

Only two endpoints deserve special comment. The first is death from lung cancer, for which risks of 10.64 (active) and 2.41 (passive) were observed. The confidence interval for the risk with passive smoking was enormously wide (0.45 to 12.83), and the point estimate of risk was higher than that in any of over 20 other, larger, studies on the issue.⁶ I have claimed elsewhere that misclassification of active smoking state can explain the average relative risk for passive smoking of about 1.3-1.5 seen in epidemiological studies.⁷ I retain this view but have never stated that it explained the figure in the Scottish study, of 2.41, to which chance has clearly contributed substantially.

The other endpoint is ischaemic heart disease, for which risks of 2.27 (active) and 2.01 (passive) were observed. Although the risk with passive smoking is significant (95% confidence interval 1.21 to 3.35) and the lower confidence limit is slightly above the bias expected, I do not find this convincing evidence of a true effect of passive smoking. This is partly because the significance level is not high, bearing in mind the number of endpoints studied; and partly because the point estimate of relative risk for passive smoking is difficult to reconcile with that for active smoking, bearing in mind that smokers have much higher active and passive exposure to the constituents of smoke, in the form of both mainstream and sidestream smoke, than do passively exposed non-smokers. More evidence is clearly needed here. The American Cancer Society million person study

accumulated 153 deaths from lung cancer and many thousands of deaths from ischaemic heart disease in non-smokers. The effect of passive smoking on lung cancer has been looked into.¹ It is a pity that its effect on ischaemic heart disease has not.

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- 1 Lee PN. Passive smoking and cardiorespiratory health in Scotland. *Br Med J* 1989;299:742 (16 September).
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AUTHORS' REPLY.—Our calculations are neither incorrect nor misleading. Mr Lee is attempting to show how large a bias can be introduced into estimates of relative risk for passive smokers due to active smokers misclassifying themselves as non-smokers. In doing so he has produced biases that are excessive because we can show his assumptions are false. His main mistake has been to assume that the "true" relative risk for lung cancer is the same for male and female smokers (his table I). Also, although the extent of smoking denial for our study is not known, we can put an upper boundary on it.

Our original study estimated the relative risk of lung cancer among active smokers as 8.49 for men and 3.33 for women.¹ Table I shows, under Mr Lee's assumptions, that "observed" relative risks for active smokers would be larger for women than for men. This is incompatible not only with what we have observed but also with all other reports we know of. Thus his assumption that the same "true" relative risk holds for both men and women

TABLE 1—"Observed" relative risks for active and passive smokers for varying denial rates of smoking*

Rate of denial (%)	Relative risks for active smoking		Relative risks for passive smoking	
	Men	Women	Men	Women
1	10.34	16.20	1.53	1.15
2	6.90	13.42	1.74	1.25
3	5.14	11.53	1.57	1.34
4	4.10	9.99	1.95	1.42
6	2.88	7.89	2.06	1.54
8	2.20	6.48	2.11	1.63
10	1.76	5.45	2.15	1.70

* Assuming "true" relative risks of 1.0 for passive smoking and 20 for active smoking.

TABLE II—Relative risks found in study¹ compared with "true" relative risks for active smokers and "observed" relative risks for passive smokers*

Endpoint	Active smokers				Passive smokers	
	Men		Women		Both sexes	
	Study finding	"True" relative risk	Study finding	"True" relative risk	Study finding	"Observed" relative risk
Infected phlegm	4.03	6.0	3.82	5.0	1.34	1.14
Persistent phlegm	4.23	6.0	3.93	5.0	1.19	1.14
Dyspnoea	1.65	1.9	1.37	1.4	1.09	1.03
Hypertension	2.95	5.0	4.15	5.0	1.21	1.13
Angina	2.13	2.7	1.44	1.5	1.11	1.05
Major abnormality in electrocardiogram	1.57	1.8	0.92	1.1	1.27	1.02
All causes of death	1.85	2.0	1.87	2.0	1.27	1.04
Ischaemic heart disease	1.36	3.0	2.89	3.0	2.01	1.07
Lung cancer	8.49	20.0	3.33	4.0	2.41	1.26
All causes of death related to smoking	1.90	3.0	2.45	3.0	1.30	1.07

* Assuming 2% of smokers deny smoking. The results for both sexes combined have been adjusted for sex using weights $N_1N_2/(N_1+N_2)$, where N_1 and N_2 are observed numbers of exposed and unexposed subjects.

is untenable. Also, if we accept Mr Lee's theoretical range of possibilities for the rates of denial of cigarette smoking then the outcomes become even more unlikely. For each rate of denial of 4% and over suggested by Mr Lee the relative risk for male active smokers is progressively well below that observed in our study (table I). Above a denial rate of 8% the "observed" relative risk for male passive smokers exceeds that for active smokers. Our data are, however, compatible with denial rates of up to 2% and a "true" relative risk of 4 for female smokers.

Mr Lee questions the extent to which misclassification can explain all the reported relative risks for active and passive smoking seen in our study. Table II shows the relative risks for active smokers found in our study for each endpoint and the "true" relative risks with which these are compatible, assuming a rate of denial of smoking of 2%. For example, the relative risks for all causes of death associated with active smoking are 1.85 for men and 1.87 for women. These figures are compatible with a "true" relative risk of 2, given a denial rate of 2%. The figure of 5 that Mr Lee quotes in his letter may be appropriate for some of the endpoints used but certainly not for all.

The final two columns of table II show the passive smoking relative risks found in our study for each of the endpoints compared with those that could have occurred through the type of bias Mr Lee attributes to our study. In particular, the differences are quite noticeable for the four categories of mortality. Thus misclassification can bias estimates of relative risk for passive smokers that use assumptions compatible with our estimates for active smokers. The size of these biases does not, however, explain our passive smoking results.

What is striking about our results is their consistency across a wide range of endpoints in addition to lung cancer and especially for ischaemic heart disease. This is supported by our findings of a dose-response relation for each of these. Even though Mr Lee reaffirms his view that misclassification of active smoking state can explain the average risk of lung cancer with passive smoking, we welcome his implication that the effect of passive smoking on ischaemic heart disease is worth further investigation.

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Congenital malformations

SIR.—In her editorial on congenital malformations Professor Eva Alberman comments on the excess rate of deaths from malformations, particularly neural tube defects, in infants of mothers born in Pakistan.¹ In the studies referred to only perinatal deaths were considered. Many neural tube defects in this country are now detected by prenatal screening programmes, and women may opt for termination of the pregnancy when found to have an affected fetus,² so these studies may not reflect the true incidence of neural tube defects. Asian women tend to book later for their antenatal care,³ and this may account for the high contribution of neural tube defects to perinatal mortality: second trimester screening would be available to a relatively smaller proportion of Asian women. Furthermore, they may find termination of pregnancy unacceptable on religious grounds.⁴ We have investigated the overall incidence of neural tube defects by ascertaining all those affected fetuses detected by prenatal screening with ultrasonography, as well as all those found in the perinatal period. We have also tried to determine factors that may be important in explaining any racial differences in the incidence.

We reviewed the maternity ultrasonography department records, neonatal and labour registers, and necropsy reports from January 1980 until the end of December 1987 in one district general hospital to ascertain all fetuses, stillbirths, and neonates with a neural tube defect. The maternal notes were then inspected to determine the date of booking for antenatal care, if and when an ultrasound scan was performed, and whether a termination of pregnancy was offered.

In the Pakistani population there were 11 neural tube defects in a total of 3777 births (2.91 per 1000); there were 32 neural tube defects in 28 834 births to white women (1.11 per 1000) (table).

Incidence of neural tube defects in fetuses and babies of white and Pakistani women, 1980-7

	White women	Pakistani women
Detected by routine ultrasound scan	17	5
Pregnancy terminated	17	4
Pregnancy continued		1
Not detected by routine scan	15	6
Scan not available	12	3
Not detected by scan	2	1
Booked too late for scan	1	1
Did not attend for scan		1
Total neural tube defects	32	11
Total births	28 834	3 777
Incidence per 1000 births	1.11	2.91

Routine examination with ultrasound was introduced only in 1984 and hence was not available to many of the women included in this study. The incidence of neural tube defects in the Pakistani population was significantly higher than that in the white population ($p=0.013$, Fisher's exact two tailed test; relative risk 2.62, 95% confidence interval 1.19 to 5.34). One woman in each group booked too late for routine prenatal screening, and one Pakistani woman failed to attend for the scan. These numbers are small, but it is of note that the mean gestation at which these women booked was 18.2 weeks in the Pakistani group as compared with 14.3 weeks in the white group.

Six of the 11 Asian babies with neural tube defects were born to women with a consanguineous marriage.

We have shown that there is a real increased incidence of neural tube defects in the Pakistani population, with late booking and reluctance to terminate an affected pregnancy contributing minimally to the increased incidence found in perinatal deaths. Changes in customs are difficult to encourage but may well occur spontaneously as

accumulated 153 deaths from lung cancer and many thousands of deaths from ischaemic heart disease in non-smokers. The effect of passive smoking on lung cancer has been looked into. It is a pity that its effect on ischaemic heart disease has not.

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Arrey SM2 SDA

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AUTHORS' REPLY.—Our calculations are neither incorrect nor misleading. Mr Lee is attempting to show how large a bias can be introduced into estimates of relative risk for passive smokers due to active smokers misclassifying themselves as non-smokers. In doing so he has produced biases that are excessive because we can show his assumptions are false. His main mistake has been to assume that the "true" relative risk for lung cancer is the same for male and female smokers (his table I). Also, although the extent of smoking denial for our study is not known, we can put an upper boundary on it.

Our original study estimated the relative risk of lung cancer among active smokers as 8.49 for men and 3.33 for women. Table I shows, under Mr Lee's assumptions, that "observed" relative risks for active smokers would be larger for women than men. This is incompatible not only with what we have observed but also with all other reports we know of. Thus his assumption that the same "true" relative risk holds for both men and women

TABLE 1—"Observed" relative risks for active and passive smokers for varying denial rates of smoking*

Rate of denial (%)	Relative risks for active smoking		Relative risks for passive smoking	
	Men	Women	Men	Women
1	10.34	16.20	1.53	1.15
2	6.90	13.42	1.74	1.25
3	5.14	11.33	1.87	1.34
4	4.10	9.99	1.95	1.42
6	2.88	7.19	2.06	1.54
8	2.20	6.48	2.11	1.63
10	1.76	5.45	2.15	1.70

* Assuming "true" relative risks of 1.0 for passive smoking and 20 for active smoking.

TABLE 2—Relative risks found in study compared with "true" relative risks for active smokers and "observed" relative risks for passive smokers*

Endpoint	Active smokers				Passive smokers	
	Men		Women		Both sexes	
	Study finding	"True" relative risk	Study finding	"True" relative risk	Study finding	"Observed" relative risk
Infected phlegm	4.03	6.0	3.32	5.0	1.34	1.14
Persistent phlegm	4.23	6.0	3.93	5.0	1.19	1.14
Dyspnoea	1.65	1.9	1.37	1.4	1.09	1.03
Hypersecretion	2.95	5.0	4.15	5.0	1.21	1.13
Asthma	2.13	2.7	1.44	1.5	1.11	1.05
Major abnormality in electrocardiogram	1.57	1.8	0.92	1.1	1.27	1.02
All causes of death	1.35	2.0	1.87	2.0	1.27	1.04
Ischaemic heart disease	1.36	3.0	2.59	3.0	2.01	1.07
Lung cancer	5.49	20.0	3.33	4.0	2.41	1.26
All causes of death related to smoking	1.90	3.0	2.45	3.0	1.30	1.07

* Assuming 2% of smokers deny smoking. The results for both sexes combined have been adjusted for sex using weights N_1/N_2 , where N_1 and N_2 are observed numbers of exposed and unexposed subjects.

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Humble, C., Croft, J., Gerber, A., Casper, M., Hames, C.G. and Tyroler, H.A., "Passive Smoking and 20-Year Cardiovascular Disease Mortality among Nonsmoking Wives, Evans County, Georgia," American Journal of Public Health 80(5): 599-601, 1990.

This report stems from a prospective 20-year follow-up of a group of rural women, both blacks and whites, in Evans County, Georgia. The 1990 Humble, et al. report specifically followed-up 328 white and 185 black women who had never smoked and whose husbands also either never smoked or were current smokers. Determination of the smoking status of both the wives and their spouses was assessed at baseline in 1960. The primary endpoint was the broad category of cardiovascular disease (CVD) mortality. During the 20-year follow-up, 147 deaths occurred, 76 of which were attributed to CVD. After controlling for age, cholesterol, blood pressure and body mass, a relative CVD risk of 1.59 was reported for nonsmoking women married to smokers compared to women married to nonsmokers. A relative risk of 1.39 was reported for all cause mortality. Neither value was statistically significant.

Criticisms

1. The women's smoking status was determined in 1960. Although some data on smoking status were available from 1967, important changes in smoking could nevertheless have occurred during the 20-year follow-up. Some indication of this is from the authors' acknowledgement that 25% of the husbands who reported smoking in 1960 had changed their smoking status by 1967.

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2. No data were available for remarriage, and this may have influenced the exposure status of the wives. This possibility was acknowledged by the authors.

We lack data to examine whether exposure status changed during follow-up due to remarriage.
(p. 600)

3. Especially because this is a quite recent article, it is notable that the authors stated in their introductory comments that research up to that time had failed to demonstrate a clear relationship of ETS exposure with heart disease.

. . . the risk for all CVD mortality associated with passive smoking among non-smokers has not been previously investigated. Recent studies of risks for coronary heart disease, stroke, or all cause mortality associated with passive smoking generally have reported weak and/or statistically nonsignificant results. (p. 599)

4. Data were presented separately for blacks, high social status whites and low social status whites. For none of these individual groups was a statistically significant relationship reported between spousal smoking habits and cardiovascular disease mortality. Even when all of the groups were considered together, any possible relationship between ETS exposure and total CVD mortality did not reach statistical significance.

5. When only those causes of death which the authors considered to be "smoking-related" were considered, then there was

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still no statistically significant relationship reported, either when considering any of the subgroups or all subjects together.

6. Any possible relationship between ETS exposure and CVD mortality is highly questionable, because it appeared to take opposite directions, depending on the social status of the subjects. In particular, in high social status whites exposed to ETS, the reported relative risk for CVD was elevated. On the other hand, in low social status whites, this relative risk was reportedly lower. It bears noting, however, that no statistically significant was reported concerning these observations.

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Public Health Briefs

Passive Smoking and 20-Year Cardiovascular Disease Mortality among Nonsmoking Wives, Evans County, Georgia

CHARLES HUMBLE, MS, JANET CROFT, MPH, ANN GERBER, MSPH, MICHELE CASPER, MSPH,
CURTIS G. HAMES, MD, AND HERMAN A. TYROLER, MD

Abstract: The association of passive smoking and cardiovascular disease (CVD) mortality was assessed in a cohort of 513 rural, married Black and White women who were disease-free and self-described as never-smokers at baseline in 1960. Over a 20-year period, 76 of 147 total deaths were attributed to CVD. Relative risk estimates adjusted for age, cholesterol, blood pressure, and body mass from proportional hazards models were 1.59 for CVD (95% CI = 0.99, 2.57) and 1.39 (CI = 0.99, 1.94) for all cause mortality among women with husbands who smoked cigarettes. (*Am J Public Health* 1990; 80:599-601.)

Introduction

Cardiovascular diseases account for about one-half of all deaths in the United States annually.¹ Although active smoking is well-established as a CVD risk factor,² the risk for all CVD mortality associated with passive smoking among nonsmokers has not been previously investigated. Recent studies of risks for coronary heart disease,³⁻⁸ stroke,^{4,5} or all cause mortality^{7,9,10} associated with passive smoking generally have reported weak and/or statistically nonsignificant results.

The 20-year mortality experience of nonsmoking women in Evans County, Georgia was used to assess the association of passive smoking with CVD and all cause mortality. This is the first report that includes data on both Blacks and Whites and on the consistency of self-reported smoking behaviors over time.

Methods

In 1960-61, 92 percent of all residents ages 40-74 years and a 50 percent sample of individuals ages 15-39 years in Evans County, Georgia participated in a cardiovascular disease study that included risk factor measurements, complete physical examinations, and a demographic and medical history interview.¹¹ Detailed descriptions of the Evans County study design and the 20-year mortality follow-up of the cohort have been reported elsewhere.¹¹⁻¹³ At baseline, 554 (82 percent) White and 389 (83 percent) Black women,

among a total of the 1,127 women ages 40-74, reported that they had never smoked. The present study was restricted to the 328 White women and 185 Black older women who had never smoked and were married to male examinees who reported they either had never smoked or were current smokers at baseline. Women married to ex-smokers were excluded from the analyses as the probability for misclassification of these subjects' own smoking habits and those of their husbands was judged to be higher than for spouses of never smokers.¹⁴ A second survey of study subjects in 1967 provides data on the stability of reported smoking status.

Vital status was determined as of May 1, 1980. Underlying cause of death was abstracted from death certificates with codes 390-456 (ICD 8th Revision) defining CVD. All CVD mortality was chosen as an endpoint given the limitations of death certificate data and the small number of deaths attributed to each specific CVD entity.¹⁵ Three subjects who did not have follow-up information were excluded.

Analyses for White women were stratified by social status because of its inverse relationship with smoking status and CVD mortality in this cohort.¹⁶ White women were divided into high social status and low social status groups based on the median of the McGuire-White index of social status for all Evans County Whites. This index, based on occupation, level of education, and source of income of the head of household, was developed for use in rural settings.¹⁵ Since only 5 percent of the Black women in the Evans County population had a social status score above the median for Whites, Blacks were not stratified by social status. Exposure to passive smoking was defined by husband's smoking status (current, never) at the time of the baseline interview.

Mean baseline characteristics by passive smoke exposure were compared using t-tests. Cox proportional hazards models¹⁶ were used to estimate the association of passive smoking with time to all CVD, smoking-related CVD, and all cause mortality in this population while adjusting for age alone and for age, systolic blood pressure, serum cholesterol, body mass index (BMI), and a quadratic term for BMI. Relative risks (RR) and 95% confidence intervals (CI) were calculated using the SAS proportional hazards (PHGLM) modeling procedures,^{17,18} and the statistical significance of trends was tested using a method proposed by Rothman.¹⁹ Constancy of the relative risks over time was verified before the proportional hazards were modeled.

Results

Among nonsmoking married women, there were 179 (55 percent) of 328 White women and 117 (63 percent) of 185 Black women whose husbands reported current cigarette

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TABLE 1—Mean and Standard Error of Baseline Characteristics by Passive Smoking Status of Nonsmoking Wives, Ages 40–74 Years, Evans County, Georgia, 1960–81

	White Women				Black Women	
	High Social Status*		Low Social Status*		Exposed	Unexposed
	Exposed	Unexposed	Exposed	Unexposed		
N	(78)	(83)	(101)	(66)	(117)	(68)
Age	51.9 ± 1.0	54.9 ± 0.9	52.1 ± 0.8	53.9 ± 0.9	50.3 ± 0.7	55.5 ± 1.0
Systolic Pressure	145.5 ± 3.1	150.6 ± 2.9	151.6 ± 2.9	157.6 ± 4.3	170.6 ± 3.4	176.5 ± 5.0
Diastolic Pressure	88.4 ± 1.6	90.6 ± 1.4	92.2 ± 1.3	93.1 ± 1.7	103.1 ± 1.9	103.9 ± 2.5
Serum Cholesterol	231.9 ± 4.9	237.5 ± 4.5	227.0 ± 4.4	235.7 ± 7.3	216.5 ± 3.9	216.2 ± 4.6
Body Mass Index	26.3 ± 0.6	26.4 ± 0.6	27.0 ± 0.5	28.6 ± 0.9	29.2 ± 0.6	30.0 ± 0.9

*Based on the median of McGuire-White scores for all White subjects.

smoking behavior. Among both Black and White women there were no statistically significant ($p < 0.05$) differences by passive smoking status for systolic or diastolic blood pressure, serum cholesterol or body mass (Table 1). However, passively exposed Black women and high social status White women were younger on average than nonexposed wives by 5.2 years (95% CI = 3.0, 7.6) and 3.0 years (95% CI = 0.3, 5.5), respectively. For all Whites combined, nonexposed women were also more likely to be above the median SES (socioeconomic status) level than passively exposed women (55.7 percent vs 43.6 percent).

Comparison of self-reported smoking status in 1960 and 1967 showed 98 percent of wives again reported themselves as never having smoked in 1967. Similarly, 98 percent of never smoking husbands maintained their reported status in 1967 while 25 percent of husbands who smoked in 1960 described themselves as non-smokers in 1967.

Age-adjusted RRs for all CVD, smoking-related CVD, and all cause mortality among passively exposed wives were elevated in Blacks and high social status Whites and for all subjects combined (Table 2). The opposite relationship of mortality with passive smoking status was found for low social status White women. Adjustment for other established CVD risk factors (blood pressure, cholesterol, and BMI) generally caused modest elevations of the risk estimates (Table 3) but as with the age-adjusted estimates, the confidence intervals for all subject groups included unity. A trend in risk over level of husband's smoking as reported in 1960 was only seen among high social status Whites; RRs for both total and smoking-related CVD mortality among wives whose husbands smoked <10, 10–20,

TABLE 2—Age-adjusted Relative Risks and 95% Confidence Intervals for Total CVD, Smoking-related CVD, and All-Cause Mortality for Wives Exposed to Passive Smoke in Evans County, Georgia, 1960–80

Cause of Death		All Subjects	Blacks	Whites	
				HSS**	LSS**
CVD Total	RR	1.34	1.69	1.66	0.60
	95% CI	0.84, 2.21	0.83, 3.46	0.64, 4.32	0.27, 1.34
Smoking-related	RR	1.29	1.57	1.67	0.61
	95% CI	0.79, 2.10	0.73, 3.37	0.64, 4.36	0.25, 1.47
All cause	RR	1.31	1.34	1.80	0.72
	95% CI	0.95, 1.82	0.79, 2.28	0.94, 3.47	0.41, 1.27

*ICD8 codes 410–456

**High social status

**Low social status

TABLE 3—Relative Risks* and 95% Confidence Intervals for Total CVD, Smoking-related CVD, and All Cause Mortality for Wives Exposed to Passive Smoke in Evans County, Georgia, 1960–80

Cause of Death		All Subjects	Blacks	Whites	
				HSS**	LSS**
CVD Total	RR	1.59	1.78	1.97	0.79
	95% CI	0.99, 2.57	0.86, 3.71	0.72, 5.34	0.32, 1.96
Smoking-related	RR	1.54	1.68	1.97	0.82
	95% CI	0.93, 2.55	0.76, 3.71	0.72, 5.34	0.31, 2.15
All cause	RR	1.39	1.33	1.97	0.87
	95% CI	0.99, 1.94	0.78, 2.28	1.00, 3.90	0.48, 1.59

*Hazards ratios adjusted for age, diastolic blood pressure, total serum cholesterol, body mass index (BMI = kg/meter²), and BMI²

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**High social status

**Low social status

and >20 cigarettes per day as compared to wives of nonsmokers were 1.02, 2.11, and 2.55, respectively (p for trend < 0.06). A marginally significant ($p < 0.09$) trend in risk for all CVD and smoking-related CVD over crude levels of duration of exposure was also apparent only among high social status White women.

Discussion

These data suggest an elevation of risk for death from CVD and all causes among non-smoking married women whose husbands described themselves as current smokers at the beginning of a 20-year follow-up period. Our findings for Blacks are the first report associating CVD with passive smoking in this racial group. Our observations that social status may modify the effect of passive smoke exposure may be due to chance, but a similar pattern of results for coronary heart disease (CHD) has been reported in other studies of passive smoking. Nonsignificant ($p > 0.05$) two-fold RRs for CHD among passive smokers were reported from studies of middle-class and upper-middle-class women⁶ and men⁷ while CHD risk was significantly but more modestly increased (RR = 1.2) among a much larger sample of predominantly blue collar Washington County, Maryland women.⁸ No increased risk for CHD was reported among public hospital patients whose husbands smoked in four British hospital regions.⁹

It is unlikely that these results can be explained by a change in smoking habits since the minimum age of these women in 1960 was 40. We lack data to examine whether exposure status changed during follow-up due to remarriage. The absence of elevated risk among exposed low social status

White women may reflect a failure of our passive exposure index to measure exposure within the lower social stratum. Power to test for small differences in effect of passive smoking by race or social standing was lacking as were data to evaluate the role of other variables such as alcohol use or physical activity. Taken together with the results of previous studies^{4-8,10} and laboratory results suggesting that passive smoke exposure causes decreases in energy production in the mitochondria of heart muscle²⁰ and increased platelet aggregability in nonsmokers,²¹ our results support the health hazards of exposure to passive smoke.²⁰

ACKNOWLEDGMENTS

This work was supported by NIH grants 5-T32-HL07055-13 and 2-R01-ML03341 (Meri Award). The authors thank Judson Wells for his helpful comments. The results described here were originally presented at the annual meeting of the Cardiovascular Behavioral Medicine, Epidemiology and Biostatistics Training Session in San Francisco, California, on March 29, 1989.

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Community Impact of a Localized Smoking Cessation Contest

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Abstract: The present study assessed the effectiveness of a localized community contest timed to coincide with a statewide smoking cessation contest. Follow-up interviews were conducted with 218 local contest participants and 198 participants from the statewide contest. Overall cessation impact (participation rate \times abstinence) was 0.39 percent for the local contest and 0.09 percent for the statewide contest. Localized community contests offered in conjunction with statewide or national campaigns may represent cost-effective methods of reaching large numbers of smokers. (*Am J Public Health* 1990;80:601-603.)

Introduction

Contests to promote smoking cessation appear to represent cost-effective means of producing quit attempts in

community settings.¹⁻³ Quit smoking contests have been offered on a number of occasions as part of the smoking intervention in the Minnesota Heart Health Program (MHHP), a 10-year research and demonstration project intended to reduce the prevalence of heart disease.^{4,5}

Several smoking cessation contests have been timed to coincide with the Great American Smokeout conducted annually by the American Cancer Society (referred to as "D-Day" in Minnesota). The present study examined contest participation and outcome for samples of Twin Cities area residents in the 1984 Minnesota D-Day contest. Participants from one of the intervention communities (Bloomington) were compared with a random sample of those from other Minneapolis suburbs (not within the immediate Bloomington area). It was hypothesized that the overall impact of a contest, measured by participation and abstinence outcome, offered in conjunction with specific localized community recruitment and prizes would be greater than that of the statewide contest alone.

Method

Subjects were recruited for a statewide D-Day contest during the Fall of 1984. Recruitment began August 25, 1984

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Lee, P.N., Chamberlain, J. and Alderson, M.R., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," British Journal of Cancer 54: 97-105, 1986.

Lee, et al. performed a hospital-based case-control study in England that was initially designed to examine disease risk in relation to cigarette smoking. However, as the study progressed, it was also decided to collect information on ETS exposure, the primary estimate of which was based on spousal smoking habits. However, questions were also asked about other possible ETS exposure sources (at home, at work, during daily travel, and during leisure time) from which a combined index was estimated.

The cases were hospital patients who had diagnoses of either lung cancer, chronic bronchitis, ischemic heart disease or stroke. The controls were hospital patients without these diseases and were matched to cases on the basis of sex, age, and several other variables.

Lee, et al. reported that ETS exposure was not statistically related to ischemic heart disease, nor to any of the three other diseases considered in the study (lung cancer, chronic bronchitis, and stroke). It was concluded that any potential risk of ETS "is at most small, and may not exist at all." The authors discuss several limitations with previous studies of ETS.

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Criticisms

1. For neither males nor females, no statistically significant relationship of ETS exposure with heart disease was reported.

2. The authors characterized their data as not indicating an increased disease risk associated with ETS.

3. The authors note several major flaws in conclusions from previous studies of ETS and disease risk. These flaws relate to low levels of ETS to which nonsmokers are exposed, unreliable exposure data, misclassification of smoking status, and specific scientific criticisms of individual studies.

4. The sample size was very small.

5. This was a case-control study and suffers from common problems with such studies, including difficulties in establishing appropriate groups and controlling for potential confounding variables.

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Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases

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Summary In the latter part of a large hospital case-control study of the relationship of type of cigarette smoked to risk of various smoking-associated diseases, patients answered questions on the smoking habits of their first spouse and on the extent of passive smoke exposure at home, at work, during travel and during leisure. In an extension of this study, an attempt was made to obtain smoking habit data directly from the spouses of all lifelong non-smoking lung cancer cases and of two lifelong non-smoking matched controls for each case. The attempt was made regardless of whether the patients had answered passive smoking questions in hospital or not.

Amongst lifelong non-smokers, passive smoking was not associated with any significant increase in risk of lung cancer, chronic bronchitis, ischaemic heart disease or stroke in any analysis.

Limitations of past studies on passive smoking are discussed and the need for further research underlined. From all the available evidence, it appears that any effect of passive smoke on risk of any of the major diseases that have been associated with active smoking is at most small, and may not exist at all.

Study of hospital in-patients

In 1977 a large hospital case-control was initiated to study the relationship of the type of cigarette smoked to risk of lung cancer, chronic bronchitis, ischaemic heart disease and stroke. This study was carried out in 10 hospital regions in England; interviewing ended in January 1982. The original questionnaire did not include questions on passive smoking as it was not considered an important issue in 1977. However, in 1979 it was decided to extend the questionnaire to cover passive smoking for married patients for the last four regions to begin interviewing. Subsequently, in 1981, following publication of the papers by Hirayama (1981) and by Trichopoulos *et al.* (1981) claiming that non-smoking wives of smokers had a significantly greater risk of lung cancer than non-smoking wives of non-smokers, it was decided to increase the number of interviews of married lung cancer cases and controls. The extended questionnaire was then administered to these patients in all hospitals where interviewing was still continuing.

Follow-up study of spouses of non-smoking hospital in-patients

In 1982, after interviewing of hospital in-patients had been completed, it was decided to carry out a follow-up study. In this study, an attempt was

made to interview the spouses of all of the married hospital in-patients with lung cancer who reported never having smoked, as well as of two married non-smoking controls for each of these index lung cancer cases. The follow-up study was intended partly to compare information on spouses' smoking habits obtained first-hand with that obtained second-hand during the in-patient interviews, and partly to obtain some data on spouses' smoking habits for those patients who had not answered passive smoking questions in hospital.

This paper concentrates solely on the issue of passive smoking in lifelong non-smokers. Results relating to type of cigarette smoked are described elsewhere (Alderson *et al.*, 1985), while a detailed report, available on request from PNL, considers the overall findings from this case-control study.

Methods and response

Study of hospital in-patients

For each of the 4 index diagnoses (lung cancer, chronic bronchitis, ischaemic heart disease and stroke), the intention was to interview 200 cases and 200 matched controls in each of the eight sex/age cells (i.e. male or female, and aged 35-44, 45-54, 55-64 or 65-74). This gave a target of 12,800 patients, though for some categories (e.g. young female chronic bronchitis) this would be unattainable. Patients were selected from medical (including chest medicine), thoracic surgery, and radiotherapy wards. Controls were patients without one of the four index diagnoses, individually matched to cases on sex, age, hospital region and,

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when possible, hospital ward and time of interview. Subsequently, when final discharge diagnoses became available, they were used to reallocate cases and controls as necessary. Patients without a final diagnosis kept their provisional diagnosis. Where changes in case-control status occurred, patients were regrouped into new case-control pairs as appropriate. With the assistance of Sir Richard Doll and Mr Richard Peto, non-index diagnoses were classified as follows:

- class 1A 'definitely not smoking associated'
- class 1B 'probably not smoking associated'
- class 2A 'probably smoking associated'
- class 2B 'definitely smoking associated'

Controls with no final diagnosis were considered class 1B. Overall, there were 12,693 interviews carried out which resulted in 4,950 pairs with class 1 controls and 730 pairs with class 2 controls.

There were 3,832 interviews of married cases and controls where the passive smoking questionnaire was completed. In order to avoid substantial loss of data, due to one member of a pair not being married or not completing the passive smoking questionnaire, it was decided to ignore matching when analysing the passive smoking data and to compare each index group with the combined controls. Numbers by sex and case-control status are given in Table I.

Table I Numbers of married hospital in-patients completing passive smoking questionnaires

	Male	Female	Total
Lung cancer	547	245	792
Chronic bronchitis	182	84	266
Ischaemic heart disease	286	221	507
Stroke	161	137	298
Controls			
Class 1A and 1B*	839	713	1,552
Class 2A and 2B*	268	149	417
Total	2,283	1,549	3,832

*Other diseases were classified by degree of smoking association - class 1A: definitely not, class 1B: probably not, class 2A: probably, class 2B: definitely.

In the passive smoking part of the questionnaire, patients were asked when the marriage started; if and when it had ended; the number of manufactured cigarettes per day smoked by the spouse both during the last 12 months of marriage and also at the period of maximum smoking during the marriage; and whether the spouse ever regularly smoked hand-rolled cigarettes, cigars or a pipe during the marriage. For second or subsequent marriages, questions related to the first marriage to

give the longest latent interval between exposure and disease onset. The patients were also asked to quantify, according to a four-point scale (a lot, average, a little, not at all), the extent to which they were regularly exposed to tobacco smoke from other people prior to coming into hospital in 4 situations: at home; at work; during daily travel; during leisure time. In the main questionnaire, detailed questions were asked on smoking habits and on a whole range of possible confounding variables.

Follow-up study of spouses of non-smoking hospital in-patients

From the hospital study there were 56 lung cancer cases who reported being lifelong non-smokers, who were married at the time of interview and who were not known to have been married previously. In a follow-up to the main study, an attempt was made to interview the spouses of these 56 cases and also the spouses of two life-long non-smoking controls for each case, individually matched for sex, marital status and 10-year age group and, as far as possible, hospital. Where multiple potential controls in the same hospital were available, those interviewed nearest in time to the case were selected. Where suitable controls in the same hospital were not available, those in the nearest hospital were chosen.

Because names and addresses of the patients were not recorded in the hospital study, it was necessary to go back to the hospital both to obtain this information and also to get permission to interview their spouses. Following some refusals both by the hospital and by the spouses, successful interviews were obtained from spouses of 34 cases (10 wives and 24 husbands) and 80 controls (26 wives and 54 husbands) whose condition was definitely or probably not related to smoking.

Interviewing was carried out between July 1982 and August 1983. The spouses were asked about their consumption of manufactured cigarettes, cigars and pipes (a) nowadays, (b) during the year of admission of the patient or (c) maximum during the whole of the marriage. The spouses were not asked about the smoking habits of the index patient. The spouses were also asked questions on age, occupation, social class and a range of other potential confounding factors.

Statistical methods

The statistical methods are based on classical procedures for analysis of grouped data derived from case-control studies (Breslow & Day, 1980). In general, the material has been examined as a $2 \times K \times S$ table, with K representing the levels of the

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risk factor of interest and S the number of strata used to take account of potential confounders.

Results presented are for the combined strata and show the relative risk (Mantel-Haenszel estimate) together with the significance of its difference from a base level (risk 1.0), and/or the dose-related trend. In analyses of the data collected in hospital, comparisons are made between cases with a particular index disease and all the controls with diseases definitely or probably not related to smoking. Six simple indices of passive smoke exposure were considered in these latter analyses, (i)-(iv) exposure at home, at work, during travel, during leisure, (v) spouse smoking manufactured cigarettes in the last 12 months, and (vi) spouse smoking manufactured cigarettes in the whole of the marriage. Bases for (ii) are reduced as not all patients worked. In addition, a combined index of passive smoke exposure was calculated by the unweighted sum of the four individual exposure indices (i)-(iv), counting 'not at all' as 0, 'little' as 1, 'average' as 2 and 'a lot' as 3.

Results

Lung cancer

The follow-up study concerned 56 lung cancer cases and 112 matched controls who reported never

having smoked in their hospital interview. Of these, there were 47 cases (15 male and 32 female) and 96 controls (30 male and 66 female) for whom some information on smoking habits of their spouses was available. Of these 143 patients, information on spouse smoking was available both from the spouse and from the patient for 59 (41%), from the spouse only for 55 (38%) and from the patient only for 29 (20%). Table II shows the estimated age-adjusted relative risk of lung cancer in relation to spouse smoking during the whole of the marriage, by sex, source of data, and period of smoking. None of the 9 relative risks shown in the table are statistically significant. When data for both sexes and both sources are considered, the estimated relative risks in relation to spouse smoking are close to 1 (1.11). For individual sexes or sources, where numbers of cases and controls are smaller, relative risks vary more from unity, but no consistent pattern is evident. Similar conclusions were reached, when analyses were based on smoking during the year of hospital interview. Here, the overall relative risk was again close to 1 (0.93 with limits 0.41-2.09).

Table III summarises concordance between spouse's manufactured cigarette smoking habits as reported directly and indirectly for the 59 patients with data from both sources. Discrepancies were seen for 9 spouses (15%) in respect of smoking at some time during marriage and in the case of 2

Table II Relationship between spouse's manufactured cigarette smoking during the whole of the marriage and risk of lung cancer among lifelong non-smokers (standardised for age)

Sex of patient	Spouse did not smoke		Spouse smoked		Relative risk (95% limits)
	Cases	Controls*	Cases	Controls*	
<i>Based on interviews of the spouse in follow-up study (114 patients):</i>					
Male	5	13	5	13	1.01(0.23-4.41)
Female	5	16	19	38	1.60(0.44-5.78)
Combined	10	29	24	51	1.33(0.50-3.48)
<i>Based on interviews of the index patient in hospital (88 patients)</i>					
Male	7	15	5	7	1.53(0.37-6.34)
Female	9	17	8	20	0.75(0.24-2.40)
Combined	16	32	13	27	1.00(0.41-2.44)
<i>Based on both sources of information (143 patients)^b</i>					
Male	7	16	8	14	1.30(0.38-4.39)
Female	10	21	22	45	1.00(0.37-2.71)
Combined	17	37	30	59	1.11(0.51-2.39)

*Only controls included in follow-up study considered. *In this analysis the spouse was counted as a smoker if reported to be so either directly, by the spouse during follow-up interview, or, indirectly, by the patient in hospital. Note that the 59 patients for whom information on spouse smoking was available from both sources are included in all 3 analyses.

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Table III Concordance between spouse's manufactured cigarette smoking habits as reported directly and indirectly

	Sex of patient/case control status				
	Male		Female		Total
	Cases	Controls	Cases	Controls	
Spouse a smoker sometime in marriage according to:					
Subject and spouse	2	6	5	13	26
Only subject	1	0	0	3	4
Only spouse	1	1	3	0	5
Neither	3	11	1	9	24
% subject/spouse agreement	71%	94%	67%	88%	85%
Spouse a smoker during year of hospital interview according to:					
Subject and spouse	1	6	2	4	13
Only subject	0	0	0	1	1
Only spouse	1	0	0	0	1
Neither	5	12	7	20	44
% subject/spouse agreement 86%	86%	100%	100%	96%	97%

spouses (3%) in respect of smoking during the year of hospital interview. There was no consistent pattern in the direction of discrepancy.

Table IV summarises the results of analyses carried out relating 7 indices of passive smoke exposure recorded in the hospital interviews to risk of lung cancer among lifelong non-smokers. Here the controls used for comparison are all never smoking patients with diseases classified as definitely or probably not associated with smoking who completed the passive smoking questionnaire.

Overall the results showed no evidence of an effect of passive smoking on lung cancer incidence among lifelong non-smokers. In male patients, relative risks were increased for some of the indices but numbers of cases were small and none of the differences approached statistical significance. In females, where numbers of cases were larger, such trends as existed tended to be negative and indeed were marginally significantly negative ($P < 0.05$) for passive smoking during travel and during leisure. For the combined sexes no differences or trends were statistically significant at the 95% confidence level; such trends as existed tending to be slightly negative. The relative risk in relation to the spouse smoking during the whole of the marriage was estimated to be 0.80 for the sexes combined, with 95% confidence limits of 0.43 to 1.50. Standardisation for working in a dusty job, the variable apart from smoking found to have the strongest association with lung cancer risk in the analyses described in Alderson *et al.* (1985), did not

affect the conclusion that passive smoking was not associated with risk of lung cancer among never smokers in our study.

Chronic bronchitis, ischaemic heart disease and stroke

Analyses similar to that shown in Table IV for lung cancer were also carried out for chronic bronchitis, ischaemic heart disease and stroke. Illustrative results for two of the indices are presented in Table V.

No significant relationship of any index of passive smoking to risk of the 3 diseases was seen. For the sexes combined, the relative risk in relation to the spouse smoking during the whole of the marriage was 0.83 for chronic bronchitis (95% confidence limits 0.31-2.20), 1.03 for ischaemic heart disease (limits 0.65-1.62) and 0.90 for stroke (limits 0.53-1.52). For stroke there was, in both sexes, an approximate 2-fold increase in risk for patients with a combined passive smoke index that was high (score of 5 to 12) compared with those where it was low (score of 0 or 1). However, numbers of cases with a high score were low (14 males and 7 females) and even for the sexes combined, the relative risk estimate of 2.18 was not statistically significant (limits 0.86-5.48). In interpreting this finding, it should be noted that active smoking was not found to be clearly related to stroke in the main study (Alderson *et al.*, 1985), rendering a two-fold increase in relation to passive smoking *a priori* unlikely.

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Table IV Relationship between various indices of passive smoke exposure and risk of lung cancer among lifelong non-smokers (standardised for age and, for spouse smoking, whether the marriage was ongoing or ended)

Passive smoke exposure index/level	Male patients			Female patients			Sexes combined		
	Cases	Controls	R	Cases	Controls	R	Cases	Controls	R
At home									
Not at all	9	101	1	21	192	1	30	293	1
Little	2	21	1.22	6	65	0.92	8	86	0.98
Average/a lot	1	11	1.11	5	61	0.81	6	72	0.86
At work									
Not at all	3	40	1	12	113	1	15	153	1
Little	6	29	3.24	3	26	1.18	9	55	1.82
Average/a lot	1	29	0.46	0	19	0.0	1	48	0.19
During travel									
Not at all	8	101	1	28	238	1	36	339	1
Little	3	16	2.06	2	51	0.33	5	67	0.64
Average/a lot	0	13	0.00	0	13	0.00	0	26	0.00
						Trend (negative) $P < 0.05$			
During leisure									
Not at all	3	45	1	15	116	1	18	161	1
Little	4	48	1.12	14	107	1.05	18	155	1.06
Average/a lot	5	39	3.18	2	95	0.18	7	134	0.59
						Trend (negative) $P < 0.05$			
Combined index*									
Score 0-1	1	27	1	10	75	1	11	102	1
Score 2-4	7	55	4.34	5	61	0.63	12	116	1.08
Score 5-12	2	15	3.20	0	21	0.00	2	36	0.50
Spouse smoked man. cigs. in last 12 months									
No	10	105	1	20	193	1	30	298	1
Yes	2	29	0.96	11	122	0.76	13	151	0.79
Spouse smoked man. cigs. in whole of marriage									
No	7	93	1	13	89	1	20	182	1
Yes	5	40	2.47	19	229	0.55	24	269	0.80

*Based on sum of 0 = not at all, 1 = little, 2 = average, 3 = a lot for at home, at work, during travel, during leisure.

Discussion

Over the past 4 years there has been considerable research interest in the relationship between passive smoking and risk of lung cancer in nonsmokers. While some studies have claimed a positive effect (Hirayama, 1981; Trichopoulos *et al.*, 1981; Correa *et al.*, 1983; Garfinkel *et al.*, 1985; Gillis *et al.*, 1984; Knott *et al.*, 1983), others (Buffler *et al.*, 1984; Chan, 1982; Garfinkel, 1981; Kabat and Wynder, 1984; Koo *et al.*, 1984) have found no significant relationship. Relative risks of lung cancer for non-smoking women married to smokers compared to non-smoking women married to non-smokers range from somewhat over 2 in the Trichopoulos and Correa studies to around 0.75 in

the Buffler and Chan studies. The weighted relative risk from these studies has been estimated by us as approximately 1.3. While there is, therefore, a tendency for a small positive association between passive smoking and lung cancer, recent reviews of these data (Lee, 1984; Lehnert *et al.*, 1984) have concluded that overall there is no reliable scientific evidence of a causal relationship between passive smoking and lung cancer. In these reviews a number of general points have been made.

First, dosimetric studies have shown that, in cigarette-equivalent terms, passive smoking only results in a relatively small exposure to the non-smoker. Hugod *et al.* (1978), for example, showed that even under quite extreme conditions the time taken for a non-smoker to inhale the equivalent of

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Table V Relationship between two indices of passive smoke exposure and risk of chronic bronchitis, ischaemic heart disease and stroke among lifelong non-smokers (standardised for age and, for spouse smoking, whether the marriage was ongoing or ended)

Passive smoke exposure index/level	Male patients			Female patients			Sexes combined		
	Cases	Controls	R	Cases	Controls	R	Cases	Controls	R
Chronic bronchitis									
Combined index*									
Score 0-1	1	27	1	7	75	1	8	102	1
Score 2-4	2	55	0.83	4	61	1.05	6	116	1.00
Score 5-12	1	15	1.90	1	21	1.03	2	36	1.30
Spouse smoked man cigs. in whole of marriage									
No	8	93	1	4	89	1	12	182	1
Yes	1	40	0.34	13	229	1.22	14	269	0.83
Ischaemic heart disease									
Combined index*									
Score 0-1	15	27	1	23	75	1	38	102	1
Score 2-4	12	55	0.43	9	61	0.59	21	116	0.52
Score 5-12	3	15	0.43	4	21	0.81	7	36	0.61
Spouse smoked man cigs. in whole of marriage									
No	26	93	1	22	89	1	48	182	1
Yes	15	40	1.24	55	229	0.93	70	269	1.03
Stroke									
Combined index*									
Score 0-1	5	27	1	19	75	1	24	102	1
Score 2-4	10	55	1.24	10	61	0.86	20	116	0.97
Score 5-12	4	15	1.77	7	21	2.44	11	36	2.18
Spouse smoked man cigs. in whole of marriage									
No	18	93	1	19	89	1	37	182	1
Yes	6	40	0.84	49	229	0.92	55	269	0.90

*Based on sum of 0 = not at all, 1 = little, 2 = average, 3 = a lot for at home, at work, during travel, during leisure.

one cigarette would be 11 hours as regards particulate matter and 50 hours as regards nicotine. Similarly, Jarvis *et al.* (1985) have shown that the increase in salivary cotinine in relation to passive smoke exposure is less than 1% of that in relation to active smoke exposure. Extrapolating linearly from the 10-fold relative risk of lung cancer in relation to active smoking would therefore predict a relative risk in relation to passive smoking less than 1.1, while a quadratic extrapolation, as suggested by Doll and Peto (1978) would predict a lower risk still. The conflict between the dose and the claimed response is particularly clear for the results of Hirayama (1981) who found a similar effect on lung cancer for passive smoking as for active smoking of 5 cigarettes a day.

Second, all the studies suffer from weak exposure data, most studies only obtaining information on the spouse's smoking habits and none obtaining objective data by measurement of ambient levels of smoke constituents in the air of the home or

workplace and/or of concentrations of constituents in body fluids.

Third, no studies adequately take into account the possibility that misclassification of active smokers as non-smokers may have consistently biased relative risk estimates upward. Active smokers have a high relative risk of lung cancer and spouses' smoking habits are positively correlated. Because of this, it can be shown that if a relatively small proportion of smokers deny smoking, this results in an *apparent* elevation in risk of lung cancer in 'non-smokers' married to smokers compared to 'non-smokers' married to non-smokers, even when no *true* effect of passive smoking exists. A demonstration that this source of bias is of real importance can be found in the study of Garfinkel *et al.* (1985). Based on unvalidated smoking data taken from hospital notes, a relative risk of lung cancer in relation to husband's smoking at home of 1.66 was calculated, with relative risks of at least 1.3 seen in relation to each

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level of husband's cigarette smoking and in relation to husband's cigar and pipe smoking. When additional sources of information on smoking habits were used, the overall relative risk was reduced to a marginally significant 1.31 with an elevated risk only really discernible in relation to heavy cigarette smoking by the husband. Even here, it is notable that the elevation in risk was not evident when smoking data were obtained from the subject or her spouse directly, but was only evident when the data were obtained from the daughter or son or another informant, i.e. from those people who were less likely to have known the full smoking history. The lower relative risk may still have arisen wholly or partly as a bias resulting from misclassification of smoking habits.

Fourth, many of the studies are open to specific criticisms. For example, the conclusion of Gillis *et al.* (1984) that male lung cancer deaths in non-smokers rose from 4 per 10,000 in those not exposed to passive smoke to 13 per 10,000 in those who were exposed was based on a total of only 6(!) deaths and was not statistically significant. Also the claim by Knott *et al.* (1983) of a relationship between passive smoking and lung cancer in non-smoking women was based simply on the observation that the proportion of female non-smoking lung cancer patients living together with a smoker exceeded the proportion of male smokers as reported in the previous microcensus, ignoring *inter alia* the fact that in many families women live with more than just their husbands.

In the present study no significant relationship of passive smoking to lung cancer incidence in lifelong non-smokers was seen, either in the analyses based on the information collected in hospital or in subsequent inquiry of the spouses or both. It must be pointed out, however, that the number of lung cancer patients who had never smoked was rather small so that, though our findings are consistent with passive smoking having no effect on lung cancer risk at all, they do not exclude the possibility of a small increase in risk, though the upper 95% confidence limit of 1.50 for the estimate of 0.80 (Table IV) in relation to the spouse smoking during the whole of the marriage is not consistent with some of the larger increases claimed by Hirayama (1981, 1984) Trichopoulos *et al.* (1981, 1983) and Correa *et al.* (1983).

Though the number of lung cancer patients who had never smoked is small, varying around 30-50 depending on the analysis, this number is not very different from that reported in a number of other studies, e.g. the findings of Correa *et al.* (1983) were based on only 30, while those of Trichopoulos *et al.* (1981), even when updated (Trichopoulos *et al.*, 1983) were based on only 77. The difficulty of obtaining an adequate sample size is underlined

when one considers that in our study the 44 never smoking lung cancer patients who completed passive smoking questionnaires in hospital were extracted from a total of 792 lung cancer patients. It would need a very large research effort to increase precision substantially, and even then one would have to take care that the magnitude of any biases did not exceed the magnitude of the effect one was looking for.

The two major prospective studies which have so far reported findings on passive smoking (Hirayama, 1981; Garfinkel, 1981) were not actually designed to investigate this issue and, as a result, could only use spouse's smoking as an index of exposure. Our study, on the other hand, though not able to monitor exposure objectively, as would have been preferable, was able to look at passive smoking in a wider context, by asking about the extent of exposure at home, at work, during travel and at leisure. Although the answers to these questions were subjective, and could have exhibited some bias, their inclusion perhaps allows greater confidence in the conclusions.

It was interesting that, of the 59 patients for whom spouse's cigarette smoking habits were obtained from both the spouse and the patients, there were 9 (15%) patients for whom there was disagreement as to whether the spouse had been a smoker at some time during the marriage. It seems reasonable to suppose that some of these were in fact smokers and may have been erroneously classified as non-smokers had only one source of information been used. It was also noteworthy that there was quite a strong correlation in our study between active and passive smoking. As illustrated in Table VI, current smokers were considerably more likely to be exposed to passive smoke exposure at home (from sources other than their own cigarettes) than were never or ex-smokers. As noted above, this correlation, coupled with some misclassification of smokers as non-smokers, may spuriously inflate the estimate of risk related to passive smoking. It is important to carry out further studies to obtain more accurate information on reliability of statements about smoking habits because of this possibility of bias.

Little other evidence is available concerning the relationship between passive smoking and risk of the other smoking-associated diseases in (adult) non-smokers and much of this is open to criticism. In his original paper, Hirayama (1981) presented relative risks of death for various diseases for non-smoking women according to the husband's smoking habits. Based on a total of 66 deaths, a slight positive trend for emphysema and asthma was not significant, while, based on a total of 406 deaths, no indication of a trend at all was seen for ischaemic heart disease. In a later paper, based on

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Table VI Relative odds of having passive smoke exposure at home according to patient's own manufactured cigarette smoking habits (standardised for age base - combined class 1 and 2 controls)

Own smoking habits	Relative odds (95% confidence limits)	
	Male	Female
Never	1	1
Ex	1.25 (0.86-1.81)	1.26 (0.86-1.85)
Current	4.00 (2.67-5.94)	2.51 (1.74-3.62)
Chi-squared for trend (2df)	57.81	25.34
P	<0.001	<0.001

only a further 88 ischaemic heart disease deaths. Hirayama (1984) reported a slight positive trend in risk, but this was not statistically significant. Garland *et al.* (1985), in a small prospective study, reported a 15-fold higher risk of ischaemic heart disease in non-smoking Californian women whose husbands were current or former smokers compared with those whose husbands were never smokers, but this enormous and implausible relative risk was only significant at the 90% confidence level and had very wide confidence limits, being based on only 2 deaths in women whose husbands were current smokers. Sandler *et al.* (1985), in a case-control study carried out in North Carolina, reported a strong relationship between risk of cancer of all sites and passive smoking. This study has been criticised by Lee (1985) who notes that it is basically implausible that passive smoking should increase risk of cancers not associated with active smoking. Lee also criticised the method of analysis, showing that no association with cancer risk would be found if a more standard method of analysis was used. Vanderbroucke *et al.* (1984), based on a 25 year follow-up of 1,070 Amsterdam married couples, recently reported that passive smoking was associated with some decrease in total mortality.

There is evidence indicating that young children whose parents smoke have an excess incidence of respiratory symptoms and some reduction in pulmonary function. Reviewing this evidence, Lee (1984) noted that the interpretation of the association is fraught with difficulties and that other possible explanations, including social class related factors, parental neglect, nutrition, cross-infection and smoking during pregnancy, had not been taken into account adequately, so that a causal effect of passive smoking could not be inferred. The relevance of these findings to chronic bronchitis or other diseases in adults is in any case not clear.

Our analyses showed no significant effect of

passive smoking on lifelong non-smokers as regards risk of chronic bronchitis, ischaemic heart disease or stroke. In all the analyses relating the various indices of passive smoke exposure to these diseases, no significant differences were seen and slight decreases in risk were as common as slight increases.

While more data would be desirable for these diseases, lung cancer continues to be the major smoking associated disease for which passive smoking comes under suspicion. Since all the difficulties of carrying out good research have clearly still not yet been overcome, further research is certainly needed. Our findings appear consistent with the general view, based on all the available evidence, that any effect of passive smoking on risk of lung cancer or other smoking-associated diseases is at most quite small, if it exists at all. The marked increases in risk noted in some studies are more likely to be a result of bias in the study design than of a true effect of passive smoking.

Any views expressed in this paper are those of the authors and not of any other person or company.

This study was funded by the Tobacco Research Council (now Tobacco Advisory Council), to whom we are most grateful. Dr Alderson was the holder of the Cancer Research Campaign endowed Chair of Epidemiology at the Institute of Cancer Research during the period of the study design and field work.

Mr. I. Marks from Research Surveys of Great Britain provided advice in the planning phase and was responsible for the interviewers' vital contribution to the study. We thank the many clinicians at the 46 participating hospitals who permitted us to contact their patients and all the patients and spouses who answered the questions.

Dr R. Wang, who held a British Council award for the period 1980-1983, as well as a number of other colleagues provided useful advice at various stages of the study.

Mrs B.A. Forey provided invaluable assistance in carrying out the statistical analyses.

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Martin, M.J., Hunt, S.C. and Williams, R.R., "Increased Incidence of Heart Attacks in Nonsmoking Women Married to Smokers," Presented at the Annual Meeting of the American Public Health Association, Abstract, 1986.

This study is available only in abstract form, based on a presentation at a 1986 meeting of the American Public Health Association. The study was based on the self-reported health history and smoking status of a group of parents of Utah high school students. Women between the ages of 30 and 59 who had never smoked, were classified according to whether their husbands were smokers, never smokers or exsmokers. Of the 7,115 nonsmoking women, 23 reported having had a heart attack. The authors reported that, compared to women whose husbands had never smoked, women married to smokers had a relative risk of 4.4. After statistically controlling for family history of coronary heart disease, hypertension, diabetes, weight, alcohol intake and amount of exercise, this relative risk was 3.4. Both values were reported as statistically significant. The authors also suggested that the risk may have increased with length of exposure, and that women married to former smokers also had an elevated risk, although not as great as for women married to current smokers. The authors concluded:

These results suggest that women married to smokers have an increased risk of heart attacks as a result of exposure to environmental tobacco smoke.

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Criticisms

1. This study is available only in the form of an unpublished abstract, which provides very few details on which to base an evaluation.

2. The source of medical information about these nonsmoking women was highly questionable. It was based only on self-reported health history. There were no reviews of medical records or other evaluation of these self-reports that might have been useful in assessing their accuracy or reliability.

3. The sample size was very small, consisting of only 23 self-reported heart attacks.

4. The credibility of the entire study is called into question when one considers that the relative risk that Martin, et al. report to be associated with exposure to ETS is several times greater than what the Surgeon General claims is the overall heart disease risk in smokers.

5. No data were available on possible ETS exposure outside of the home, such as the workplace.

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Presented, Annual Meeting, American Public Health
Association, (October 1, 1986), 1 p.

Michael J. Martin, MD (University of California, San Francisco), Steven
C. Hunt, PhD, and Roger R. Williams, MD (University of Utah)

INCREASED INCIDENCE OF HEART ATTACKS IN NONSMOKING WOMEN MARRIED TO SMOKERS.

To investigate the incidence of heart attacks in never-smoking women exposed to environmental tobacco smoke, the authors analyzed data collected from 18,344 parents (9,172 spouse pairs) of Utah high school students. Each parent had been asked to report on his or her own health history, including the occurrence and age of onset of a heart attack, stroke, coronary bypass surgery, hypertension, diabetes, and cancer. All never-smoking women ($N = 7,115$) who were between the ages of 30 and 59 and for whom there was information on the husband's smoking status were included in the current study. There were 941 women married to current smokers, 950 women married to former smokers, and 5214 women married to never-smokers. A total of 23 heart attacks were reported by these women. Compared to women married to never-smokers, the women married to current smokers were 4.4 ($p < .01$) times as likely to have had a heart attack. When a proportional hazards model was used to control for other known risk factors (family history of CHD, hypertension, diabetes, weight, alcohol intake, and amount of exercise) the relative risk was still 3.4 ($p < .01$). There seemed to be an increased risk with an increased length of exposure; women married to former smokers had less of an increased risk ($RR = 1.9$) than women married to current smokers ($RR = 4.4$). These results suggest that women married to smokers have an increased risk of heart attacks as a result of exposure to environmental tobacco smoke.

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Palmer, J.R., Rosenberg, L. and Shapiro, S., "Passive Smoking and Myocardial Infarction in Women," Abstract, CVD Epidemiology Newsletter No. 43, 29, Winter 1988.

This is a hospital-based case-control study which examined 366 female myocardial infarction (MI) cases in relation to spousal smoking status. A relative MI risk of 1.2 was reported for nonsmoking women married to smokers. Also, elevated MI risks were reported in smoking women, depending on the smoking status of their husband. In women who smoked less than 25 cigarettes per day, the reported relative MI risk was 2.9 if the husbands did not smoke, compared to 3.9 if the husbands did smoke. For heavy smoking women, these estimates were 6.3 and 8.3, respectively. The authors stated that these trends were "not accounted for by the known risk factors for MI." It was further stated that these results support an elevation of MI risk in relation to spousal smoking, and that these results "are unlikely to be explained by selection or information bias."

Criticisms

1. This is an abstract only, apparently not subject to peer review, appearing only in a set of abstracts submitted for presentation at a cardiovascular disease epidemiology meeting sponsored by the American Heart Association.

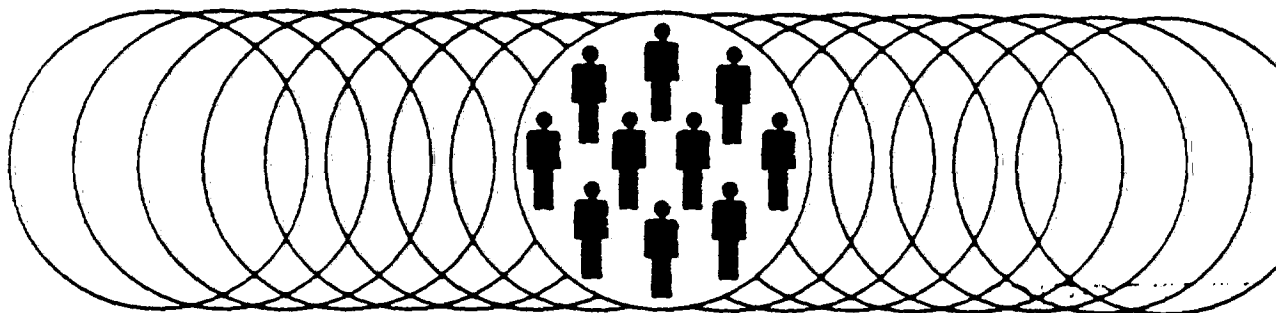
2. Since this is an abstract only, few details are available on which to evaluate the study.

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3. Although several figures for relative risks were reported, there was no information indicating that these figures were evaluated for statistical significance.

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CVD EPIDEMIOLOGY NEWSLETTER



COUNCIL ON EPIDEMIOLOGY

 American Heart Association

Number 43
Winter 1988

Milton Z. Nichaman, M.D., Sc.D.
Editor

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Abstracts Submitted for the 28th Conference on
Cardiovascular Disease Epidemiology

Santa Fe, New Mexico March 17-19, 1987

Abstracts of all papers submitted to the Program Committee of the Council on Epidemiology for the 28th Annual Conference on Cardiovascular Disease Epidemiology are reprinted below in the order they were received, except for those deleted at the request of the author. For additional information about any of the abstracts see the index of author correspondents immediately following the last abstract.

1

DOES LOWERING OF CHOLESTEROL WITH CHOLESTYRAMINE DECREASE THE INCIDENCE OF HYPERTENSION IN HYPERCHOLESTEROLEMIC MEN? THE LNC CORONARY PRIMARY PREVENTION TRIAL (CPPT)
Lars G. Ekelund, RP McMahon, FS Whaley, EH Corder, CL Rubenstein, The University of North Carolina at Chapel Hill, NC.

Hypertension (HTP) is often associated with high cholesterol levels. We studied 2595 normotensive men [systolic pressure (SBP) ≤ 140 and diastolic pressure (DBP) ≤ 90 mmHg] in the CPPT to determine if lowering LDL-C decreases the risk of HTP (SBP ≥ 140 or DBP ≥ 90 or BP medication). Baseline examinations included a treadmill test and assessment of risk factors and were repeated annually. The incidence of HTP after 5 years of follow-up was 11.3% (159/1297) in the placebo group compared to 9.7% (119/1298) in the cholestyramine group. This difference was significant, $p=0.003$, testing with a logistic regression model including standard HTP risk factors as covariates. Further analyses revealed that decrease in LDL-C was the factor explaining the treatment effect. The relative risk of HTP (RR-HTP) was significantly ($p=0.01$) associated with the reduction in LDL-C controlling for covariates. A 40 mg/dl and a 80 mg/dl decrease in LDL-C corresponded to a RR-HTP of 0.71 and 0.51 respectively. We conclude that cholestyramine induced lowering of LDL-C is associated with a decrease in the risk of HTP, raising the possibility of LDL-C being a modifiable risk factor for hypertension.

4

THE 19-YEAR DECLINE OF CORONARY HEART DISEASE AND STROKE IN THE HONOLULU HEART PROGRAM
Dwayne Reed and Charles MacLean.
Honolulu Heart Program, Honolulu, HI

Since 1966, the Honolulu Heart Program has monitored the incidence and mortality rates for coronary heart disease (CHD), and stroke among a cohort of 8006 men of Japanese ancestry living in Hawaii. During 19 years of follow-up there were 702 cases of total definite CHD of which 458 were fatal, and 443 cases of stroke of which 193 were fatal. There was a 18% decrease in age-adjusted CHD mortality rate and a 20% decrease in the incidence of definite CHD. The decrease in mortality rates was less than that for US white males, and was not statistically significant. During the same time period, there was a 64% decrease in stroke mortality rates and a 65% decrease in the incidence of total stroke. The decrease in mortality rates was greater than that for US white males and was statistically significant. The mortality rates of these vascular diseases appear to reflect the changes in total incidence for this cohort.

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PASSIVE SMOKING AND MYOCARDIAL INFARCTION IN WOMEN. Julie R. Palmer, 83
Lynn Rosenberg, Samuel Shapiro.
Slone Epidemiology Unit, Brookline, MA

In a hospital-based case-control study of past oral contraceptive use and myocardial infarction (MI) in women aged 20 to 64, information is being obtained on the smoking habits of subjects' husbands in order to evaluate the effect of passive exposure to sidestream cigarette smoke on risk of MI. We conducted an interim analysis of data from 336 married cases and 799 married controls. With a reference category of nonsmoking women married to nonsmoking men, the relative risk estimate for nonsmoking women whose husbands smoked was 1.2; for women who smoked less than 25 cigarettes per day the estimates were 2.9 (nonsmoking husbands) and 3.9 (husbands smoked); and for women who were heavy smokers, the estimates were 6.3 and 8.3, respectively. The observed trend was not accounted for by the known risk factors for MI. These results, which lend support to the hypothesis that exposure to spouses' smoking increases the risk of MI, are unlikely to be explained by selection or information bias.

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ORAL CONTRACEPTIVE USE AND MYOCARDIAL INFARCTION. Lynn Rosenberg, 84
Julie R. Palmer, Samuel Shapiro, Slone
Epidemiology Unit, Brookline, MA

A case-control study is being conducted primarily to assess whether the long-term use of oral contraceptives (OCs), after discontinuation, increases the risk of myocardial infarction (MI). In an interim analysis of data from 675 women under age 65 with first MIs and 1274 control women of similar ages, the estimated relative risks of MI for women who had used OCs for 1-4, 5-9, and 10+ years were 1.2 (95% confidence interval 0.8-1.7), 1.2 (0.8-1.9), and 1.3 (0.7-2.4), respectively. These results do not confirm a previous finding of a doubling in risk among women who had used the older OCs for at least 5 years; possibly the newer lower-dose OCs have less adverse effects on serum lipids and other cardiovascular risk factors than the older pills. For current OC users, the relative risk estimate was 2.6 (1.0-7.1); although this point estimate is compatible with the 4-fold increase in risk associated with the older pills, it is also compatible with a smaller increase, or with no increase at all.

INTERCORRELATIONS OF LIPOPROTEINS AND LOW DENSITY LIPOPROTEIN (LDL) SUBCLASS PATTERNS IN RELATION TO RISK OF MYOCARDIAL INFARCTION. Melissa A Austin, Charles E Hennekens, Jan L Breslow, Julie E Buring, Walter C Willett, Karen M Vranizan, Ronald M Krauss. Univ. of Calif., Berkeley, CA

In 230 subjects from the Boston Area Health Study, a case-control study of myocardial infarction (MI) survivors, we have shown that a predominance of small, dense LDL particles (LDL subclass pattern B by gradient gel electrophoresis) is associated with increased risk of MI with an odds ratio (OR) of 3.0 (95% CI 1.7-5.3), independent of age, sex, relative weight, LDL-cholesterol and intermediate density lipoprotein mass (IDL). Adjustment for high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) reduced the OR to 2.2 (95% CI 1.2-4.1) and 1.6 (95% CI 0.8-3.2), respectively. Because of collinearity in these models, intercorrelations of lipoproteins and pattern B were investigated. HDL-C, IDL and TG were all found to be independently related to LDL subclass pattern B, after adjustment for age, sex, relative weight, and case-control status. Biological mechanisms may simultaneously influence multiple lipoprotein variables, including LDL subclass patterns, and result in increased risk of MI.

EXERTIONAL CHEST PAIN AND RISK OF FATAL AND NON-FATAL CORONARY HEART DISEASE IN THREE OLDER POPULATIONS 87

Andrea Z. LaCroix, Jack M. Guralnik, Charles H. Hennekens, Robert B. Wallace, Adrian M. Ostfeld, J. David Curb. National Institute on Aging, Bethesda, MD

Among older people, the prognostic significance of self-reported chest pain for future myocardial infarction (MI) and coronary heart disease (CHD) death is unknown. Cohorts aged 65 and older in three communities (East Boston, MA; New Haven, CT; rural Iowa) without history of heart attack (3067 men, 5291 women) were followed for 3 years for CHD death and annually (self or proxy) reported hospitalization for MI. At baseline, chest pain on exertion was found in 6-7% of men (79/1195; 53/936; 54/936) and 6-10% of women (197/2046; 131/1435; 115/1811) in each community, respectively. Fatal and non-fatal CHD events occurred in a total of 213 men and 250 women. In East Boston and Iowa, exertional chest pain was significantly associated with risk of fatal and non-fatal CHD events combined in both men and women. Age-adjusted risk ratios for women ranged from 2.0 (95% confidence interval (CI) 1.2-3.5) in East Boston to 5.1 (95% CI 2.8-9.4) in Iowa, with men's risk ratios intermediate in these cohorts. In New Haven, the association was positive in both sexes but weaker and non-significant. These findings suggest that exertional chest pain reported by older people without previous heart attack can be an important indicator of future CHD events.

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Svendsen, K.H., Kuller, L.H., Martin, M.J. and Ockene, J.K., "Effects of Passive Smoking in the Multiple Risk Factor Intervention Trial," American Journal of Epidemiology 126(5): 783-795, 1987.

This study was based on data from men who participated in the Multiple Risk Factor Intervention Trial (MRFIT). MRFIT was not designed as a study of ETS, but rather to determine whether reducing levels of cholesterol, blood pressure, and cigarette smoking in middle-aged men would produce corresponding reductions in coronary heart disease mortality. On the basis of a "risk score" which incorporated these factors, all of the MRFIT participants were considered to be at high risk of heart disease. However, this was an overall score and did not require that all participants have high levels of all of these "risk factors." Of the total of 12,866 MRFIT subjects, the Svendsen, et al. report focused on the 1,400 who had never smoked. At entry into the study, information was collected on the wives' smoking habits, which was used as the basis for estimating ETS exposure. The men were followed for an average of seven years, during which time 13 coronary heart disease deaths occurred. Comparing nonsmoking men whose wives smoked to those whose wives did not, the relative risk for coronary heart disease death was reported to be 2.11. After statistically adjusting for several other variables, this ratio was 2.23. These ratios were not statistically significant.

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Criticisms

1. This study did not report a statistically significant effect of ETS exposure with heart disease risk.

2. The sample size was very small, being based only on 13 deaths from heart disease.

3. The exposure data may be particularly questionable, because the wives' smoking status was based on interviews with the husbands, not on direct questioning of the wives.

4. The sample size was biased, in that all of the MRFIT participants were considered to be at high risk (upper 10-15%) for heart disease, according to a risk score based on levels of cholesterol, blood pressure, and smoking. Hence, the possible relevance of the study to people in general is unknown.

5. It is possible that the husband's smoking status was misclassified at entry into the study.

6. There may be an alcohol-related bias in this study. The subjects who were classified as being ETS-exposed drank more alcohol per week than those who were classified as not being exposed to ETS.

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7. Although this study attempted to statistically control for several variables, there are a wide variety of behavioral, social, and other factors related to heart disease which are potentially uncontrolled confounding factors but that were not considered in this study.

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Original Contributions

EFFECTS OF PASSIVE SMOKING IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL

KENNETH H. SVENDSEN,¹ LEWIS H. KULLER,² MICHAEL J. MARTIN,² AND
JUDITH K. OCKENE²

Svensden, K. H. (Coordinating Centers for Biometric Research, U. of Minnesota, Minneapolis, MN 55414), L. H. Kuller, M. J. Martin, and J. K. Ockene. Effects of passive smoking in the Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1987;126:783-95.

The Multiple Risk Factor Intervention Trial (MRFIT), conducted in 1973-1982, provided a unique opportunity to study the effect of passive smoking on men whose wives smoke. MRFIT participants who reported at entry that they had never smoked tobacco products were classified according to the smoking status of their wives. Men with wives who smoked had similar mean levels of serum thiocyanate (54.3 vs. 53.9 $\mu\text{mol/liter}$, $p = 0.83$) but higher mean levels of expired carbon monoxide (7.7 vs. 7.1 ppm, $p = 0.001$). Lower levels of pulmonary function (by maximum forced expiratory volume in one second) were also observed in these men (3,493.1 vs. 3,591.9 ml, $p = 0.04$). The relative risks, for men whose wives smoked compared with men whose wives did not smoke, for the endpoints coronary heart disease death, fatal or nonfatal coronary heart disease event, and death from any cause were 2.11 ($p = 0.19$, 95% confidence interval (CI) 0.69-6.46), 1.48 ($p = 0.13$, 95% CI 0.89-2.47), and 1.96 ($p = 0.08$, 95% CI 0.93-4.11), respectively. When smokers who quit prior to entry were included in the analyses, the relative risks, for men whose wives smoked compared with men whose wives did not smoke, for the above endpoints were 1.45 ($p = 0.25$, 95% CI 0.77-2.73), 1.19 ($p = 0.29$, 95% CI 0.85-1.65), and 1.72 ($p = 0.01$, 95% CI 1.12-2.64), respectively. These relative risk estimates did not change appreciably after adjusting for other baseline risk factors. The results suggest that passive exposure to cigarette smoke may have a deleterious impact on the health of non-smokers and that nonsmokers may be at an increased risk of death through passive exposure to cigarette smoke.

coronary disease; tobacco smoke pollution

Passive smoking is defined as exposure of an individual to the air pollution resulting from another person's tobacco smoke. The products of tobacco smoke are divided

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Abbreviations: FEV₁, forced expiratory volume in

one second; MRFIT, Multiple Risk Factor Intervention Trial.

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into two components. Those directly exhaled by the smoker are called mainstream smoke, while those from the lit end of the cigarette, cigar, or pipe which are discharged into the environment are referred to as sidestream smoke. The composition of sidestream smoke (1) differs substantially from that of mainstream smoke, depending upon the different temperatures at which the substances burn and the available oxygen supply. Particulates, for example, are about 10 times greater in mainstream smoke than in sidestream smoke. After inhalation, sidestream smoke probably reaches the more distant alveolar spaces in the lung (2). Sidestream smoke also contains much more free nicotine in the gas phase, generates more carbon monoxide (1), and contains much higher concentrations of the reduced products of nitrogen including several highly carcinogenic substances (3). Most environmental tobacco smoke is from sidestream smoke, and only a very small amount is from exhaled mainstream smoke. Environmental exposures to tobacco smoke depend on the number of smokers in the area and the amount they smoke, the size of the area, and the ventilation rate.

It is now an accepted fact that cigarette smokers have an increased risk of many diseases. In recent years, there has been a growing concern that nonsmokers exposed to environmental tobacco smoke may also be at increased risk of certain diseases, especially cancer, chronic obstructive pulmonary disease, and, possibly, heart disease.

Friedman et al. (4) reported that 63.3 per cent of adults were exposed to passive

smoking for at least one hour per week. A higher percentage was exposed away from home, usually at work. Repace and Lowrey (5) have estimated that the exposure to environmental tobacco smoke of the non-smoking adult population was about 1.43 mg of tar per day. A cigarette smoker, on the other hand, can be expected to inhale about 420 mg of tar per day (14 mg of tar per cigarette for an average of 30 cigarettes per day). Thus, the dose from passive smoking is much less than the dose from cigarette smoking.

Studies on passive smoking reported to date have depended on self-reported histories of environmental tobacco smoke exposure. A workshop on the respiratory effects of environmental tobacco smoke in 1983 sponsored by the Division of Lung Diseases at the National Heart, Lung, and Blood Institute (6) noted that lack of objective measures of dose or exposure, confounding variables, methods of statistical analysis, and quantification of other variables were major concerns in the evaluation of current and future studies.

Participants in the Multiple Risk Factor Intervention Trial (MRFIT) (7) offered an unusual opportunity to study the effect of environmental tobacco smoke on men, especially in the home. Objective measures of cigarette smoking behavior, as well as other critical risk factors for cardiovascular and other diseases, were carefully monitored in a large population followed for an average of seven years. Fortunately, at entry into the study, prior to randomization, a detailed smoking history was obtained for each of the participants subsequently randomized. This history included not only their own smoking history but also that of their wives, family members, and coworkers. This trial, to our knowledge, is the first longitudinal study that was able to objectively define the participants' smoking status and possible exposure to environmental tobacco smoke. The study design was also unique because the index subjects were men who did not smoke and who were at high risk of heart disease, and the exposure in-

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dex was the smoking behavior of their wives.

MATERIALS AND METHODS

The Multiple Risk Factor Intervention Trial was a primary prevention trial designed to test the effect of a multifactor intervention program on mortality from coronary heart disease.

The design of the MRFIT has been described (7). Briefly, men aged 35–57 years were recruited in 18 US cities. They were screened to select those in the upper 10–15 per cent of a risk score distribution derived from Framingham data, based on serum cholesterol concentration, cigarette smoking, and diastolic blood pressure. Those free of overt coronary heart disease by history and resting electrocardiogram who consented to participate were randomized to either the special intervention or usual care groups. After randomization, special intervention men participated in an intensive intervention program aimed at lowering blood cholesterol by nutritional means, eliminating cigarette smoking through education and behavior modification techniques, and reducing the diastolic blood pressure of those who were hypertensive primarily by using a stepped-care drug regimen. Usual care participants were referred to their customary source of medical care with information on their risk factor status but with no advice as to intervention. Both special intervention and usual care participants were seen annually over six to eight years for risk factor measurement and a medical examination. A detailed smoking history was obtained from all participants during screening and at each annual visit.

This paper focuses on the effects of passive smoking on participants who reported that they did not smoke cigarettes, pipes, cigars, or cigarillos prior to randomization into the trial. Most analyses are restricted to men who had never smoked cigarettes. Endpoint results are shown for never smokers and all nonsmokers at entry; nonsmokers included never smokers and ex-smokers who quit prior to entry into the

study. Data on the smoking habits of the participants' wives were collected at baseline for participants who smoked and those who did not smoke. The smoking status of the wife is used as an index of passive smoking exposure for the men who did not smoke. Only a limited amount of information was collected about exposure to tobacco smoke on the job. Participants were asked the smoking status of their coworkers. The results of all analyses presented are for the special intervention and usual care groups combined. Separate analyses for each study group yielded similar results.

Measurements of smoking exposure

Serum thiocyanate was measured during screening and at each annual visit. In the planning stages of the MRFIT, it was recognized that special intervention participants who were repeatedly urged to stop or reduce smoking cigarettes might be more likely to misreport their cigarette smoking status than usual care participants. Serum thiocyanate is elevated in smokers because of the cyanide present in tobacco smoke which is metabolized to thiocyanate. The half-life of serum thiocyanate is approximately 14 days, reflecting long-term exposure to cigarette smoke.

At the third and sixth annual examinations, expired air carbon monoxide was measured, using an ecolyzer (series 2000, Energetics Science, Inc., Elmsford, NY), which permitted a visual meter reading on a 0–100 parts per million (ppm) scale. The levels of expired air carbon monoxide are directly related to carboxyhemoglobin in the blood. The half-life of elevated carboxyhemoglobin levels after exposure to environmental carbon monoxide is only two to four hours; thus, its measurement reflects only very recent exposures. Other factors, especially any incomplete combustion of carbon-containing substances, can increase environmental carbon monoxide levels and blood carboxyhemoglobin levels.

Pulmonary function testing was conducted at screening and at each annual examination using a 10-L Stead Wells

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water-filled spirometer (Warren E. Collins, Inc., Braintree, MA). The forced expiratory volume in one second (FEV_1) is defined as the volume of gas exhaled over an interval of one second, with expiration as rapid and as complete as possible. The selection of tracings for analysis was based on careful quality control standards defined prior to the current analyses. The maximum of three to five measurements meeting quality standards (maximum FEV_1), adjusted for age and height, is used to quantify pulmonary function in this paper. The quality control procedures and measurement techniques are described in detail elsewhere (8).

Endpoints

Classification of cause of death was performed by a committee of three cardiologists who were unaware of treatment assignment (special intervention/usual care) or passive smoking status. They used hospital records, physicians' reports, next-of-kin interviews, death certificates, and autopsy reports, when available. Coronary heart disease deaths were subclassified as 1) documented myocardial infarction; 2) sudden death within 60 minutes, or between one and 24 hours of symptom onset, without documented myocardial infarction; 3) congestive heart failure due to coronary heart disease; or 4) death associated with surgery for coronary heart disease. Results are also presented for the endpoint fatal or nonfatal coronary heart disease event. This endpoint includes coronary heart disease death, serial change from baseline on a resting electrocardiogram, and/or documented evidence of myocardial infarction from a review of hospital records by a panel of physicians (9).

Statistical methods

Differences in baseline characteristics and changes in risk factor levels from baseline to the sixth annual examination for men who did not smoke who had wives who smoked versus men who did not smoke who had wives who were also nonsmokers were tested for statistical significance using the

Student's *t* test (two-sided) or the 2×2 chi-square test. For comparison of measures of smoking exposure between the two groups, mean levels of thiocyanate and the maximum FEV_1 were calculated for baseline and the average of baseline and all follow-up visits. The latter results in improved precision but smaller sample size. The maximum FEV_1 means were adjusted for age and height by analysis of covariance. Mean levels of expired air carbon monoxide were calculated for year 3 and the average of years 3 and 6. Differences in the means between the two groups for thiocyanate and expired air carbon monoxide were assessed by the Student's *t* test. Differences in the adjusted means for maximum FEV_1 were assessed by analysis of covariance. Tests for a dose effect of smoking exposure were performed using regression models with number of cigarettes smoked per day reported by wife as an independent variable.

Relative risk estimates, for men whose wives smoked compared with men whose wives did not smoke, for the endpoints death from any cause, coronary heart disease death, and fatal or nonfatal coronary heart disease event were calculated using the Cox proportional hazards model (10) with Breslow's approximation (11). Results are shown both unadjusted and adjusted for age, baseline blood pressure, cholesterol, weight, education (as a measure of socioeconomic status), and drinks per week.

RESULTS

Sample size

There were 1,400 of 12,866 randomized participants who reported that they had never smoked cigarettes, pipes, cigars, or cigarillos at entry into the MRFIT. Of these never smokers, 1,245 were married; 286 to women who smoked and 959 to women who did not smoke (table 1).

Comparability of never smokers by smoking status of wife

Baseline characteristics of these 1,245 men by smoking status of wife are sum-

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marized in table 2: The two groups of men are similar with respect to age, blood pressure, and cholesterol. The average weight for men with wives who smoked was 4.2

pounds greater than that of men whose wives did not smoke ($p < 0.01$). Men whose wives smoked consumed an average of 2.1 more alcoholic drinks per week ($p < 0.01$) and had 0.5 years less formal education than men with wives who did not smoke ($p < 0.05$). Income was similar between the groups. Table 3 shows risk factor changes and the percentage of men prescribed anti-hypertensive medications at the sixth annual examination by smoking status of wife. There were no statistically significant differences between the two groups.

Comparisons of smoking exposure

Mean serum thiocyanate levels at baseline and the average of baseline and all annual follow-up visits are shown in table

TABLE 1

Frequency distribution of smoking status at entry:
Multiple Risk Factor Intervention Trial, 1973-1982

	n	%
Smokers*	9,244	71.8
Ex-smokers	2,222	17.3
Never smokers	1,400	10.9
Not married	155	1.2
Wife a nonsmoker	959	7.5
Wife a smoker	286	2.2
Total	12,866	100.0

* Includes smokers of cigarettes, pipes, cigars, or cigarillos.

TABLE 2

Mean values of selected variables at entry for 1,245 men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973-1982

	Smoking status of wife		Difference*	95% confidence interval
	Smoker (n = 286)	Nonsmoker (n = 959)		
Age (years)	47.4	47.5	-0.2	-1.0-0.6
Diastolic blood pressure (mmHg)	103.3	103.1	0.2	-0.4-0.9
Systolic blood pressure (mmHg)	152.3	150.8	1.5	-0.4-3.4
Serum cholesterol (mg/dl)	266.0	264.4	1.6	-2.3-5.5
High density lipoprotein cholesterol (mg/dl)	43.4	42.7	0.7	-0.7-2.0
Low density lipoprotein cholesterol (mg/dl)	166.5	167.1	-0.6	-5.0-3.9
Weight (lbs)	194.6	190.4	4.2	0.6-7.8
Drinks/week (n)	9.7	7.6	2.1	0.8-3.3
Education (years)	13.8	14.2	-0.5	-0.9-0.0
Income (1,000\$)	22.1	22.3	-0.1	-1.4-1.2

* Difference may not agree because of rounding.

TABLE 3

Mean change in selected variables (sixth annual minus baseline examination) for men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973-1982

	Smoking status of wife		Difference	95% confidence interval
	Smoker (n = 266)	Nonsmoker (n = 889)		
Diastolic blood pressure (mmHg)	-10.1	-9.9	-0.3	-1.7-1.1
Systolic blood pressure (mmHg)	-12.6	-13.6	1.1	-1.1-3.2
Plasma cholesterol (mg/dl)	-11.4	-11.0	-0.4	-4.7-3.9
High density lipoprotein cholesterol (mg/dl)	-1.4	-0.7	-0.7	-1.9-0.5
Low density lipoprotein cholesterol (mg/dl)	-10.8	-10.4	-0.4	-4.4-3.7
Weight (lbs)	-2.2	-2.5	0.3	-1.4-2.0
Drinks/week (n)	-2.7	-2.1	-0.6	-1.7-0.4
On antihypertensive medication (%)	66.5	62.5	4.0	-2.7-10.6

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4 by smoking status of wife. The mean thiocyanate levels are similar for the two groups, both at baseline and averaged over all visits.

Expired air carbon monoxide was measured at the third and sixth annual examinations. The average expired air carbon monoxide at the third annual examination for men whose wives smoked was 7.7 ppm compared with 7.1 ppm for men whose wives did not smoke (table 5). The difference, 0.6, is statistically significant ($p = 0.001$), as is the test for linear trend ($p = 0.03$). Similar results were obtained when the averages of the third and sixth annual carbon monoxide measurements were combined.

Men with wives who smoked had significantly lower levels of pulmonary function

at baseline as measured by the maximum FEV₁ (table 6). The mean maximum FEV₁ is 3,493.1 ml for men whose wives smoked versus 3,591.9 for men whose wives did not smoke, a difference of about 100 ml. Similar results were obtained when averaging over all visits, although the difference between the two groups was not statistically significant ($p = 0.16$).

Endpoint results for never smokers

Table 7 gives the event rates by smoking status of wife and table 8 shows the relative risk estimates (for men who did not smoke whose wives smoked compared with those whose wives did not smoke) for the endpoints death from any cause, coronary heart disease death, and fatal or nonfatal coronary heart disease event.

TABLE 4

Mean levels of thiocyanate ($\mu\text{mol/liter}$) at baseline and average over all visits for men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973-1982

Smoking status of wife	Baseline		Average over all visits	
	n	Mean	n	Mean
Nonsmoker	878	53.9	704	51.6
Smoker	264	54.3	212	52.3
1-19 cigarettes/day	125	54.0	102	51.6
≥ 20 cigarettes/day	139	54.6	110	52.9
Smoker/nonsmoker difference	0.4 (-3.7, 4.6)*		0.7 (-2.7, 4.0)	
p value for linear trend	0.99		0.55	

* 95% confidence limits.

TABLE 5

Mean expired air carbon monoxide (ppm) at the third annual visit and average over all visits for men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973-1982

Smoking status of wife	Third annual visit		Average over all visits	
	n	Mean	n	Mean
Nonsmoker	828	7.1	780	6.7
Smoker	244	7.7	228	7.1
1-19 cigarettes/day	112	7.7	106	7.1
≥ 20 cigarettes/day	132	7.8	122	7.2
Smoker/nonsmoker difference	0.6 (0.2, 1.0)*		0.5 (0.2, 0.7)	
p value for linear trend	0.03		<0.01	

* 95% confidence limits.

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TABLE 6

Mean maximum FEV₁ (ml) adjusted for age and height at baseline and average over all visits for men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973-1982

Smoking status of wife	Baseline		Average over all visits	
	n	Mean	n	Mean
Nonsmoker	514	3,591.9	257	3,491.3
Smoker	162	3,493.1	81	3,403.3
1-19 cigarettes/day	66	3,412.1	31	3,263.3
≥20 cigarettes/day	96	3,548.8	50	3,489.0
Smoker/nonsmoker difference	-98.9 (-192.4, -5.4)*		-87.8 (-210.7, 35.2)	
p value for linear trend	0.52		0.99	

* 95% confidence limits.

TABLE 7

Number of deaths from any cause and from coronary heart disease and fatal or nonfatal coronary heart disease events for men who reported never smoking cigarettes, pipes, cigars, or cigarillos, by smoking status of wife at entry: Multiple Risk Factor Intervention Trial, 1973-1982

Smoking status of wife	No. of men	Death from any cause	Coronary heart disease death	Fatal or nonfatal coronary heart disease event
Nonsmoker	959	19 (2.83)*	8 (1.19)	48 (7.28)
Smoker	286	11 (5.55)	5 (2.52)	21 (10.81)
1-19 cigarettes/day	133	3 (3.21)	1 (1.07)	8 (8.70)
≥20 cigarettes/day	153	8 (7.65)	4 (3.82)	13 (12.71)
p value for linear trend†		0.08	0.04	0.20

* Rates per 1,000 person-years.

† From Cox proportional hazards regression using number of cigarettes smoked per day by wife as a covariate.

TABLE 8

Relative risk estimates, wife who smoked compared with wife who did not smoke, and their 95 per cent confidence intervals for men who reported never smoking cigarettes, pipes, cigars, or cigarillos: Multiple Risk Factor Intervention Trial, 1973-1982

Endpoint	Relative risk	p value	95% confidence interval
Death from any cause			
Unadjusted	1.96	0.08	0.93-4.11
Adjusted*	1.94	0.08	0.91-4.09
Coronary heart disease death			
Unadjusted	2.11	0.19	0.69-6.46
Adjusted	2.23	0.17	0.72-6.92
Fatal or nonfatal coronary heart disease event			
Unadjusted	1.48	0.13	0.89-2.47
Adjusted	1.61	0.07	0.96-2.71

* Adjusted by Cox proportional hazards regression for age, baseline blood pressure, cholesterol, weight, drinks per week, and education.

As of February 28, 1982, after an average of seven years of follow-up, 11 of 286 men married to smokers had died (5.6 per 1,000 person-years) compared with 19 of 959 men

married to nonsmokers (2.8 per 1,000 person-years). There is some suggestion of a dose effect for the endpoint death from any cause, with 3.2 deaths per 1,000 person-

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years in the category wife smokes 1-19 cigarettes per day and 7.7 deaths per 1,000 person-years in the category wife smokes 20 or more cigarettes per day, although the test for a linear trend was not significant ($p = 0.08$).

The numbers are small for the endpoint coronary heart disease death, but they follow the same pattern as those for the endpoint death from any cause. The coronary heart disease death rate is 2.5 per 1,000 person-years for those whose wives smoked compared with 1.2 for those whose wives did not smoke. The test for a linear trend was significant ($p = 0.04$).

Among men with wives who smoked, there were 10.8 fatal or nonfatal coronary heart disease event endpoints per 1,000 person-years versus 7.3 per 1,000 person-years for those whose wives did not smoke. The event rate is higher for those whose wives smoked 20 or more cigarettes per day compared with those whose wives smoked 1-19 cigarettes per day, although the test for linear trend for the endpoint fatal or nonfatal coronary heart disease was not significant.

The relative risk estimates, for men whose wives smoked compared with men whose wives did not smoke, for the endpoints death from any cause, coronary heart disease death, and fatal or nonfatal coronary heart disease event are 1.96 ($p = 0.08$, 95 per cent confidence interval (CI)

0.93-4.11), 2.11 ($p = 0.19$, 95 per cent CI 0.69-6.46), and 1.48 ($p = 0.13$, 95 per cent CI 0.89-2.47), respectively. These relative risks did not change appreciably after adjusting for other baseline risk factors.

Endpoint results for all nonsmokers

Table 9 presents unadjusted and adjusted relative risk estimates, for men whose wives smoked compared with men whose wives did not smoke, for the endpoints death from any cause, coronary heart disease death, and fatal or nonfatal coronary heart disease event for all nonsmokers at entry; nonsmokers included never smokers and ex-smokers who quit prior to entry into the study. For the endpoint death from any cause, the relative risk estimate is 1.72, which differs significantly from 1.0 ($p = 0.01$, 95 per cent CI 1.12-2.64). For the endpoints coronary heart disease death and fatal or nonfatal coronary heart disease event, the relative risk estimates are 1.45 ($p = 0.25$, 95 per cent CI 0.77-2.73) and 1.19 ($p = 0.29$, 95 per cent CI 0.85-1.65), respectively. As with the analysis restricted to never smokers, adjusting for baseline risk factors did not change the relative risk estimates.

Endpoint results by smoking exposure on the job

Only a limited amount of information was collected about exposure to tobacco

TABLE 9
Relative risk estimates, wife who smoked compared with wife who did not smoke, and their 95 per cent confidence intervals for nonsmokers*: Multiple Risk Factor Intervention Trial, 1973-1982

Endpoint	Relative risk	p value	95% confidence interval
Death from any cause			
Unadjusted	1.72	0.01	1.12-2.64
Adjusted†	1.79	<0.01	1.17-2.76
Coronary heart disease death			
Unadjusted	1.45	0.25	0.77-2.73
Adjusted	1.59	0.15	0.84-3.02
Fatal or nonfatal coronary heart disease event			
Unadjusted	1.19	0.29	0.85-1.65
Adjusted	1.32	0.10	0.95-1.84

* Includes both never smokers and ex-smokers who quit prior to entry into the trial.

† Adjusted by Cox proportional hazards regression for age, baseline blood pressure, cholesterol, weight, drinks per week, education, and past smoking history.

smoke on the job. The participants were asked the smoking status of most of their coworkers. Of 1,237 never smokers, 906 (73.2 per cent) reported that most coworkers were smokers, and 331 (26.8 per cent) reported that most coworkers were nonsmokers. The relative risk for the endpoint death from any cause, for men whose coworkers smoked compared with men whose coworkers did not smoke, adjusted for age and wife's smoking status is 1.2 ($p = 0.63$, 95 per cent CI 0.5–1.8). For the endpoint coronary heart disease death, the relative risk is 2.6 ($p = 0.23$, CI 0.5–12.7), and for fatal or nonfatal coronary heart disease event, the relative risk is 1.4 ($p = 0.26$, CI 0.8–2.5).

Because of the small number of deaths, the joint impact of a spouse who smoked and coworkers who smoked was estimated only for the endpoint fatal or nonfatal coronary heart disease event. The risks for the categories wife and coworkers who smoked, wife who smoked and coworkers who did not smoke, and coworkers who smoked and wife who did not smoke relative to the category wife and coworkers who did not smoke are 1.7 ($p = 0.14$, 95 per cent CI 0.8–3.6), 1.2 ($p = 0.75$, 95 per cent CI 0.4–3.7), and 1.0 ($p = 0.99$, 95 per cent CI 0.5–1.9), respectively.

DISCUSSION

To our knowledge, this is the first longitudinal study of the relation between passive smoking and total and coronary heart disease mortality that has included measures of other major risk factors, objective monitoring of smoking behavior in a well defined population at risk, and a careful unbiased ascertainment and evaluation of causes of death. Our findings, which support the hypothesis that passive smoking is associated with an increase in morbidity and mortality among nonsmokers, are discussed below.

Thiocyanate levels did not vary by environmental tobacco exposure. This finding is similar to that reported by Friedman et al. (4). In other studies, conducted in smok-

ing chambers, a direct dose-response relation between exposure to tobacco and the cotinine levels in saliva, urine, and blood was found (12). Jarvis et al. (13) also found a positive correlation between urinary cotinine levels and self-reported exposures to sidestream cigarette smoke. Similar findings using urinary cotinine were noted by Matsukura et al. (14) and Wald et al. (15). In these studies, the differences in biochemical levels by environmental exposure were small compared with the differences between smokers and nonsmokers. For example, Wald et al. reported that the median urinary cotinine levels were 1,645 ng/ml in cigarette smokers, 6 ng/ml in nonsmokers exposed to environmental tobacco smoke, and approximately 2 ng/ml in nonsmokers not so exposed.

The increase in expired air carbon monoxide resulting from passive smoking is relatively small even if statistically significant and in and of itself is of relatively little biologic significance. The increase probably reflects exposure to environmental tobacco smoke (16). The half-life of expired air carbon monoxide is somewhat short, around four hours. The men may have been exposed to their wife's tobacco smoke at home prior to going to the clinic for their annual examination or while traveling by car to the clinic. The differences in expired air carbon monoxide or blood carboxyhemoglobin levels may have been substantially greater immediately after exposure to environmental tobacco smoke. The differences presented here also may be conservative because of the fact that the smoking status of the participant's wife was available only at baseline. By the time carbon monoxide was measured, some wives who were smokers may have quit, while others who were nonsmokers may have restarted. This type of misclassification would tend to decrease any observed difference in carbon monoxide.

The health effects of exposure to low doses of carbon monoxide are not known at present. Earlier studies have reported that individuals with cardiovascular disease

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(17, 18) have an adverse response to relatively low doses of environmental carbon monoxide. There has been controversy concerning these findings (19, 20), however, and the studies are currently being repeated in different laboratories. It is possible that transient elevations of carbon monoxide due to environmental tobacco smoke in high-risk individuals may be associated with an increased risk of heart attacks and perhaps cardiovascular deaths. The majority of sudden and unexpected deaths in the community occur at home (21). The acute precipitant of many of these heart attacks is unknown but could relate to certain indoor air pollutants. Occupational studies (20) of exposure to carbon monoxide and risk of heart attack have been equivocal in their results, as have community studies of the relation between ambient carbon monoxide and coronary heart disease mortality (22).

There have been a few studies of pulmonary function and exposure to passive smoking among adults (23-28). Three studies in the United States (23), France (24), and Holland (25) have demonstrated decreased pulmonary function among passively exposed individuals, with usually about a 100-ml difference in FEV₁ between the passively exposed compared with the nonexposed nonsmokers. A study in Hagerstown, Maryland (26), noted that 5 per cent of nonsmoking men not passively exposed and 7.1 per cent of those passively exposed had FEV₁ less than 80 per cent predicted (relative risk of 1.4). The relative risk was not statistically significantly different from one. Forty families were identified in a study of three communities in the United States in which the mother was a smoker and the father a nonsmoker (27). There was a statistically significant decrease in the mean residual FEV₁ for the fathers married to women who smoked compared with those married to women who did not smoke. The effect was, however, substantially reduced when the ex-smoking men were excluded. A recent report from the Federal Republic of Germany

(28) also failed to demonstrate any effect of passive environmental tobacco smoke on pulmonary function among a relatively young occupational cohort. There was also no apparent effect from direct cigarette smoking on either the forced vital capacity or FEV₁. Lebowitz et al. (29), in several studies in Arizona, have been unable to demonstrate any effect of environmental tobacco smoke on pulmonary function among adults who do not smoke.

The approximate 100-ml differences in the FEV₁ at baseline as noted in table 6 are consistent with those of several of the other larger studies previously discussed (23-25). It is unlikely that the relatively small differences in pulmonary function in our study can contribute substantially to chronic obstructive pulmonary disease or disability. It is possible, however, that there is a subset of individuals in whom a hypersensitivity to environmental tobacco smoke causes further progression of pulmonary disease and disability.

The excess total and coronary heart disease mortality and morbidity among MRFIT men who were exposed to environmental tobacco smoke is further evidence of a potential serious health risk for a large segment of the nonsmoking population. In the MRFIT study, 23 per cent of the men who did not smoke were exposed at home to the environmental tobacco smoke of their wives (table 1). As noted, a study by Friedman et al. (4) has suggested that up to two thirds of nonsmokers are exposed to environmental tobacco smoke. At present, the number of cancer deaths in this study is too small to allow any evaluation of the relation between environmental tobacco smoke and specific cancer and other causes of death.

Other studies have evaluated the relation between environmental tobacco smoke and lung or other cancers. Nearly all the cancer studies have been case-control studies (30-36). The cases have usually been lung or other cancers and the controls either hospital patients, community residents, or friends of the cases. Practically all the stud-

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ies show a higher prevalence of exposure to passive smoking among the cases compared with the controls. The estimated odds ratios have generally ranged from 1.5 to 2.5. The largest prospective studies have been reported from Japan (37, 38) and the United States (39). In both studies, the populations at risk were predominantly women, and the exposure sources were spouses who smoked. The study in Japan by Hirayama (37, 38) demonstrated a consistent increased risk of lung cancer and other cancers among the nonsmoking wives of men who smoked. A smaller study among nonsmoking men as index subjects also demonstrated an increased risk of lung cancer among men married to women who smoked cigarettes (40).

Our findings on total and coronary heart disease mortality and morbidity are similar to those of two other studies. A study by Garland et al. (41) specifically related environmental tobacco smoke to coronary heart disease. This study followed for an average of 10 years 695 married women, initially examined in 1972-1974, in a retirement community in California. The women were classified by the self-reported smoking status of their husbands at entry into the study. After 10 years, nonsmoking wives of current or former cigarette smokers had a higher ischemic heart disease death rate than nonsmoking wives of nonsmokers. There were, however, only two ischemic heart disease deaths among the wives of the men who never smoked, 15 among the wives of former smokers, and two among the wives of current cigarette smokers. There were no differences in age-adjusted all-cause mortality rates among the wives of never, former, or current cigarette smokers. In the longitudinal study in Japan by Hirayama (40), the wives of men who smoked cigarettes also had higher coronary heart disease mortality rates.

Several reasons for the higher overall mortality among the passive smokers have been considered. First, it is possible that some passive nonsmokers were actively smoking cigarettes. The careful chemical

measurements at baseline and follow-up would almost certainly rule out this hypothesis in the MRFIT study. Practically all cigarette smokers in the MRFIT study had thiocyanate levels over 100 $\mu\text{mol/liter}$. Among the passive smokers, 7.5 per cent had thiocyanate levels over 100 $\mu\text{mol/liter}$, compared with 7.3 per cent among the nonpassive smokers. If some men were smoking, they were equally divided among the two groups. A second hypothesis is that key risk factors may be different among passive and nonpassive smokers. The risk factors in the MRFIT trial, social-behavioral, physiologic, and biochemical, were generally similar between the passive and nonpassive smokers. These have been further reviewed in detail by Martin et al. (42). Adjustment for these other risk factors did not decrease the relative risks associated with passive smoking.

Third, certain other behavioral and social factors may be different among passive and nonpassive smokers. There is an inverse relation between education and other measures of social class and total coronary heart disease mortality (43). Similarly, there is an inverse relation between cigarette smoking and social class (44). Thus, it is more likely that passive smokers will be in the lower socioeconomic group. Adjustment for education or other measures of social class in the MRFIT trial did not reduce the increased relative risk. It is possible, although unlikely, that these adjustments did not completely deal with the potential differences in social and behavioral characteristics between the passive smokers and nonexposed men. More detailed analyses have failed to demonstrate other significant differences between these two groups.

Fourth, the passive smokers at baseline may have been less likely during the trial to change important risk factors that were related to subsequent mortality and morbidity. Analyses of risk factor changes in table 2 do not support this hypothesis.

Finally, follow-up was complete for all MRFIT men, and endpoints were assessed

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without knowledge of passive smoking status. It is very unlikely that differential ascertainment of morbidity or mortality could account for the differences in mortality between passive and nonpassive smokers that were noted.

It is always possible that other unknown factors can explain the increased relative risk of morbidity and mortality among the passive smokers. The men were obviously not randomized to wives who smoked and to those who did not smoke. A man who did not smoke married to a woman who smoked may have had other unmeasured health behaviors that increased morbidity and mortality. The consistency of the results of the current studies with many of the other case-control and longitudinal studies plus the biologic plausibility of the hypothesis based on biochemical measurements of exposure to environmental tobacco smoke and knowledge of the pathology and physiologic changes suggest that passive smoking may result in an increased morbidity and mortality among non-smokers.

Environmental tobacco smoke is a major indoor pollutant to which a substantial segment of the population is exposed (45). Obviously, the most successful method of reducing environmental tobacco smoke would be the further reduction of active cigarette smoking in the population. On the basis of these data, a continued reduction in active cigarette smoking will have a beneficial effect on both the cigarette smoker and on the nonsmoking population.

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RE: "EFFECTS OF PASSIVE SMOKING IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL"

NOTICE

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law (Title 17 U.S. Code).

Based on the Multiple Risk Factor Intervention Trial data, Svendsen et al. (1) have reported a relative risk of 1.72 for death from any cause among male passive smokers (male nonsmokers married to a smoking wife vs. male nonsmoker married to a nonsmoking wife). This risk compares with a relative risk for male active smoking (male smokers vs. male nonsmokers) of 1.66, which we calculated from the Multiple Risk Factor Intervention Trial data (2).

To the other explanations that may be offered for this surprising comparison, we wish to add an alternative possibility that may not occur to those who are not predisposed to give cigarettes the benefit of the doubt. The effect measured by Svendsen et al. may be caused by stress rather than by passive exposure to cigarette smoke.

There is considerable evidence that psychologic stress is capable of increasing the risk of developing diseases that are major causes of death. Both Type A behavior and high levels of hostility have been shown in prospective studies of human populations to predict increased risk of coronary heart disease (3) and death due to all causes (4, 5). There is additional evidence from animal studies that behavioral stress and its physiologic concomitants promote the development of both cancer (6, 7) and coronary atherosclerosis (8).

As we have previously argued (9), there are substantial grounds for believing that nonsmoking spouses of smokers are subjected to stresses arising therefrom. While the health authorities, given their convictions, have no honorable alternative, it is nevertheless stressful to the nonsmoking spouse to be told constantly that the smoking spouse is "killing herself (or himself)" by smoking cigarettes. Repeated attempts to persuade the spouse to give up smoking would be a source of contention and their failure an additional source of stress.

Also, there is reason to believe that smokers are less supportive as spouses than nonsmokers, thus creating a stress-related risk for their mates. Current female smokers are nearly three times as likely to be divorced as women who have never smoked cigarettes (rate calculated from data in reference 10). In addition, it has been demonstrated from the Framingham Heart Study data (11) that occupations, ambition, and symptoms of anger among wives were more strongly related to their husbands' coronary health outcomes than the husbands' conventional "risk factors".

More generally, the inferences drawn by Svendsen et al. may be an example of the error potential in attributing a mortality difference between two groups

of people to what is presumed by the investigators to be the only relevant average difference between them.

If there is merit in the foregoing, it may also be true that the scientific community has been incorrect in attributing to smoking the mortality rate differences so often reported for active cigarette smokers compared with nonsmokers. A hitherto undiscussed difference is that the constant admonitions that their smoking is "self-destructive" must also be stressful to the smoker, while cessation of smoking may have a placebo effect.

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Editor's Note. In accordance with Journal policy, Dr. Svendsen et al. were given the opportunity to respond to this letter, but chose not to do so.

RE: "ENVIRONMENTAL AND BEHAVIORAL DETERMINANTS OF FASTING PLASMA GLUCOSE IN WOMEN: A MATCHED CO-TWIN ANALYSIS"

Over 45 years ago, Gesell (1) described the method of co-twin control, an experimental method that was applied to the study of child development. Since monozygotic co-twins share environment as children and are genetically identical, differences between treated and untreated co-twins were interpreted to result from treatment. This method was recently extended to con-

tinuous outcomes in observational studies (2, 3). The method compares associations in an unmatched sample to associations within twin pairs (matched) to identify associations that are independent of familial variables shared by co-twins. The matched analysis consists of a multivariate linear regression forced through a zero intercept with dependent and inde-

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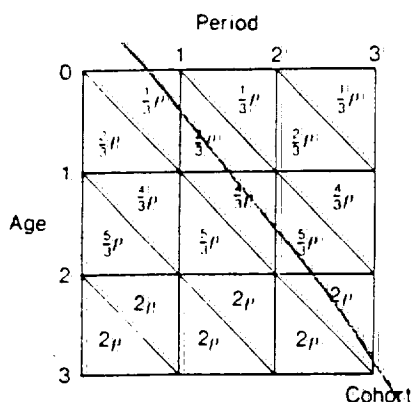


FIGURE 1. Rates for the non-linear age model, calculated in the same way as in figure 3 of Osmond and Gardner (2).

models only "work" as a result of aggregation and making assumptions of constancy of effect within an interval.

At present, we see two avenues for investigators who wish to try to estimate the separate linear effects of age, period, and cohort: 1) use a two-way table and impose a linear constraint, ignoring the overlapping of cohorts; and 2) use the individual records approach, which does not have the problem of overlapping cohorts. This approach will require a correction for potential bias brought about by the asymmetry in forcing the continuous data into a three-way table. Brown and Conolly (personal communication, 1988) have informed us of some very interesting work they are doing in this area.

Finally, in our published example on the use of individual records in the analysis of lung cancer and laryngeal cancer incidence in Scotland (3), the cohort effect is approximately quadratic and the time effect small but non-linear. Such effects cannot be induced by assuming a monotonic increasing age effect alone.

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✓ RE: "EFFECTS OF PASSIVE SMOKING IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL"

Some of the health effects of passive smoking may be small, and are best investigated in large cohort studies of persons exposed over a long period. It is unfortunate that the analysis by Svendsen et al. (1) of the unique data gathered in the course of the Multiple Risk Factor Intervention Trial (MRFIT) study is flawed, and may introduce confusion about the role of passive smoking as a risk factor in cardiovascular disease, and does not allow the investigators to fully explore the potential of passive smoking as a risk factor in other conditions.

The Svendsen paper repeatedly tests the statistical significance of the difference between the same proportion(s). For example, table 7 shows that of the 1,400 never smokers, 13 men died from coronary heart

disease and 30 from any cause, and that there were 69 fatal or nonfatal coronary heart disease events. Each group is examined for significant difference in proportions according to the wife's smoking status as if it were independent of the two other groups; in fact, the coronary heart disease death group is a subset of the two other groups, and its contribution to the calculation of relative risk is thus taken into account three times in this table. The correct analysis would have compared "death from other causes" and "nonfatal coronary heart disease events" with "death from coronary heart disease".

The misuse of statistics is compounded in table 9, when the 2,222 ex-smokers are added to the 1,400 never smokers (this is my assumption: no n's are

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given). In this analysis, the 13 coronary heart disease deaths in the never smokers are again included and the proportions to which they contribute are tested for statistical significance three more times. The appropriate analysis would have examined only the 2,222 ex-smokers in the same terms, as suggested for table 7.

The reader who is interested in outcomes other than coronary heart disease death is forced to use guesswork to subtract this effect from the other data in the tables. For example, even though we are not told the numbers of men in table 9, the much lower *p* value for "death from any cause" than in table 7 suggests that this difference is due to the contribution of the ex-smokers. Had these been analyzed separately, the difference in risk of "death from any cause" between the exposed and nonexposed ex-smokers would probably have been even more marked. This would have suggested that the men who stopped smoking were especially susceptible to second-hand tobacco smoke. A presentation of the data that did not lump

and overlap the subsets of interest would have made such speculation unnecessary.

The study by Svendsen et al. is presented as an exploration without hypothesis. This "blurred" analysis could have been avoided if this report had set out to investigate an explicit hypothesis that specified the target group and the expected endpoint. Paradoxically, focussing in on a specific research question and following the method appropriate to address that question often allows the researchers to isolate and investigate secondary or unexpected results more accurately.

REFERENCE

1. Svendsen KH, Kuller LH, Martin MJ, et al. Effects of passive smoking in the Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1987;126:783-95.

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✓ RE: "EFFECTS OF PASSIVE SMOKING IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL"

Am J Epidemiol
129 (1)
Jan. 1989 p. 2

Svendsen et al. (1) analyze data from the Multiple Risk Factor Intervention Trial (MRFIT) study and report the relative risks of various endpoint events for men who never smoked in relation to spousal smoking. They assert that their data provide "further evidence of a potential serious health risk for a large segment of the nonsmoking population" (1, p. 792). This conclusion does not appear to be supported by the data presented.

For morbidity and mortality, the relative risks are not statistically significant, except for the "all deaths" category for the group combining "never smoked" and "ex-smoker" males. Since the relative risk for "coronary heart disease deaths" was not significantly elevated for that group, the increased relative risk for "all deaths" requires some explanation before the statistics can be assumed to indicate a meaningful increase in health risk related to spousal smoking.

While the statistics alone raise serious doubt about the conclusion of increased health risk for nonsmokers exposed to environmental tobacco smoke based on spousal smoking, questions also need to be raised about the quality of the evidence on which the assessments are based, notably the nonhomogeneity between the groups based on spousal smoking classification.

The lack of homogeneity was implicit when adjustments were made for differences in some coronary heart disease risk factors, e.g., age, weight, blood pressure, and alcohol consumption, but there is no indication that the adjustment included consideration of the additive effect of multiple risk factors, as has been demonstrated in numerous other studies, notably the Framingham Heart Study. There is no indication that other coronary heart disease risk factors, e.g., family history and exercise, were considered or adjusted for. Differences in forced expiratory volume in one second (FEV₁) among the groups were also cited. The numerous confounding coronary heart disease risk factors

should not be disregarded, nor can statistical adjustments be made to eliminate their possible roles. Thus, while the MRFIT study was well designed to assess the effect of various interventions according to selected risk factors, it does not appear to have been designed to assess the environmental tobacco smoke exposure as a coronary heart disease risk factor.

Svendsen et al. observe that men whose wives smoked had "significantly lower levels of pulmonary function at baseline" (1, p. 788). The authors fail, however, to note and to interpret the data in table 6, which shows FEV₁ levels for men whose wives smoked 20+ cigarettes/day were markedly higher than those of men whose wives smoked 1-19 cigarettes/day, both at baseline and averaged over all visits. With such a notable reversal of the dose-response relation, which must be demonstrated if causal inferences are to be supported, there seems to be little basis for suggesting the possibility of any relation between pulmonary function and spousal smoking from this study.

The weakness of the evidence thus raises important questions about the conclusion that "passive smoking is associated with an increase in morbidity and mortality among nonsmokers" (1, p. 791). There is certainly no convincing demonstration that spousal smoking constitutes a "potential serious health risk" for any segment of the nonsmoking population.

REFERENCE

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✓ RE: "EFFECTS OF PASSIVE SMOKING IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL"

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129 (1)
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Svendsen et al. (1) analyze data from the Multiple Risk Factor Intervention Trial (MRFIT) study and report the relative risks of various endpoint events for men who never smoked in relation to spousal smoking. They assert that their data provide "further evidence of a potential serious health risk for a large segment of the nonsmoking population" (1, p. 792). This conclusion does not appear to be supported by the data presented.

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THE AUTHORS REPLY

Dr. Morgan (1) states that our investigation was not initiated with an explicit hypothesis. Quite the contrary. This research investigation (2) within the Multiple Risk Factor Intervention Trial (MRFIT) was carefully planned and undertaken because of the growing body of evidence that environmental tobacco smoke is a health hazard to nonsmokers. Reports that document exposure of nonsmokers to environmental tobacco smoke, such as elevated carboxyhemoglobin or cotinine in exposed persons, as well as reports of a possible relation between environmental tobacco smoke and diseases such as lung cancer, pulmonary disease, and coronary heart disease prompted this investigation. An advantage of large scale clinical trials is that data are often collected which can be used to investigate other research questions. Our research hypothesis was formulated to utilize data that were collected in the MRFIT for another purpose. The MRFIT group had collected data on smoking habits of wives for all of the 12,866 participants prior to this study of the relation between environmental tobacco smoke and disease. These data were collected not because of an interest in environmental tobacco smoke, but rather because we believed the wife's smoking behavior might impact the participant's ability to change risk factors; in particular, the ability to quit smoking for participants who were smokers.

The endpoints presented in our paper—coronary heart disease (CHD) death, fatal or nonfatal CHD event, and death from any cause—were the endpoints used for the primary MRFIT trial. Dr. Morgan is correct in observing that the CHD deaths are counted when considering the endpoints fatal or nonfatal CHD event and death from any cause. The intent was not to repeatedly test the difference between the same proportions, but to investigate if the smoking behavior of the participant's wife was related to these major MRFIT endpoints defined at the beginning of the study.

The focus of our paper (2) was on MRFIT men who had never smoked tobacco products. We repeated the table of relative risk estimates for all nonsmokers (which included never smokers and ex-smokers who quit prior to entry into the MRFIT) to provide data for comparisons with other studies which may not have such detailed lifetime smoking histories. The lower p value for the endpoint "death from any cause" in table 9 primarily reflects increased sample size and not strength of association. The hypothesis that the relative risk for this endpoint would be higher if the ex-smokers were considered alone is false. The relative risk is 1.60 ($p = 0.08$, 95 per cent confidence interval = 0.95-2.69), compared with 1.96 for never smokers (table 8) and 1.72 for all nonsmokers (table 9).

Dr. Katzenstein (3) suggests lack of homogeneity between the men who had never smoked tobacco products whose wives smoked versus those whose wives did not smoke. As noted in our paper (2) one of the strengths of the MRFIT data set was the large amount of information available regarding the biologic, social, and behavioral characteristics of the participants at entry to the trial. Baseline characteristics of men whose wives smoked and men whose wives did not smoke were similar, as we noted in table 2 of our paper

and as observed by Martin et al. (4). The significant differences were men whose wives smoked weighed 4.2 lbs (1.9 kg) more, consumed 2.1 more drinks per week, and had 0.5 years less formal education, than men whose wives did not smoke. Weight was not associated with coronary heart disease death or total mortality in the MRFIT study (5). Adjustment for baseline differences in weight, alcohol consumption, and education (used as a measure of socioeconomic status), as well as age, blood pressure, and cholesterol did not change the relative risk estimates appreciably.

Clearly, however, not every variable that might possibly differ between the husbands of women who smoke and those who do not smoke were measured. There are almost certainly social and behavioral differences between a man who is a lifetime nonsmoker married to a woman who smokes, and a man married to a woman who also does not smoke. It is possible that a man who does not smoke married to a wife who smokes makes behavioral changes because of the habit of his wife which increases his risks of death, independent of the known toxic chemicals in the environment from his wife's cigarette smoke. The ideal study, randomizing nonsmoking men to smoking or nonsmoking wives, cannot be done.

We agree with Dr. Katzenstein that the lack of a dose-response relation makes the pulmonary function data weaker. The difference in FEV₁ between men whose wives smoke 1-19 cigarettes per day and those whose wives smoke 20 or more cigarettes per day is not significant so the dose-response relation is lacking, not reversed. In view of our carbon monoxide and mortality findings, along with other studies referenced in our paper, we see no reason to alter our conclusions.

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DONNAN, G.A., MCNEIL, J.J., ADENA, M.A., DOYLE, A.E., O'MALLEY, H.M. AND NEILL, G.C., "SMOKING AS A RISK FACTOR FOR CEREBRAL ISCHAEMIA," THE LANCET, PP. 643-647, SEPTEMBER 16, 1989.

This case-control study mainly focused on active smoking as a potential risk factor for stroke. However, in what the authors described as "preliminary findings" (p. 647), data were also given on both spousal and parental smoking and stroke risk. Spousal smoking, but not parental smoking, was reported to be associated with stroke risk.

Exposure to smoking by a spouse was an independent risk factor for the whole group of cerebral ischaemia patients (relative risk 1.7 [1.2, 2.6], but this was not so for smoking by either parent (relative risk 1.2 [0.8, 1.8])). . . . The persistent nature of the risk even after cessation of smoking and the possible risk associated with passive exposure strengthens public health arguments against smoking. (pp. 643-644)

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antibodies in SCLC patients without LES has to be further investigated in a larger population to better define their possible pathogenic role. None of the myasthenic patients tested had anti-VOCC antibodies, whereas 11 LES patients had also antinicotinic receptor antibodies, which suggests the possibility of a combined myasthenic syndrome,¹ at least at the immunohistochemical level. Use of this new immunoassay to screen a larger number of myasthenia gravis patients will allow the detection of cases in which LES occurs together with myasthenia gravis.

Antigenic modulation is a common mechanism by which anti-receptor antibodies down-regulate the number of receptors expressed at the cell surface, and this effect is important for explaining the biological and clinical activity of the autoantibodies.³⁰ LES antibodies clearly recognise antigenic determinants on the VOCC which are "external" to the site where ω CTx binds, since, for the purpose of the immunoassay, this site was already occupied by the toxin. Furthermore, LES autoantibodies were not able to directly inhibit ¹²⁵I- ω CTx binding to IMR32 membranes. However, LES antibodies were able to down-regulate the expression of VOCCs in IMR32. This effect was highly specific with respect to other membrane molecules such as the α -Bgtx receptor. However, we cannot exclude the possibility that different patients synthesise different antibodies with different specificities and mechanisms of action, as in the case of antibodies against nicotinic receptors in myasthenia gravis.

We thank Dr V. A. Lennon for allowing us to perform the blind experiment, for the permission to use these results, and for help with the manuscript; Dr L. Rosenthal for helping to improve the paper; Prof G. Fumagalli for his critical suggestions; Dr F. Baggi for help with antinicotinic receptor antibody assays; and Mr P. Tinelli for technical collaboration.

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SMOKING AS A RISK FACTOR FOR CEREBRAL ISCHAEMIA

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Summary To assess whether a rigorous clinical classification, based on computerised tomography, of patients with cerebral ischaemia would identify subgroups at higher or lower risk with respect to cigarette smoking habits, a case-control study was carried out on 422 cases of first-episode cerebral ischaemia matched for age and sex with 422 community-based neighbourhood controls. Patients with ischaemic stroke due to extracranial or intracranial vascular disease were at higher risk from smoking than has previously been reported for stroke (relative risk 5.7, 95% confidence interval 2.8, 12.0) whereas those with stroke due to cardiac emboli had no excess risk associated with smoking (relative risk 0.4 [0.1, 1.8]). After cessation of smoking, the relative risk declined gradually over 10 years, at the end of which time a significant risk was still evident. This finding may imply that the risk incurred by smoking is due mainly to atheroma formation, rather than transient haematological effects. Exposure to smoking by a spouse was an independent risk factor for the whole group of cerebral ischaemia patients (relative risk 1.7 [1.1, 2.6]), but this was not so for smoking by either parent (relative

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risk 1.2 [0.8, 1.8]). These findings suggest that smoking is a more potent risk factor for the most common form of ischaemic stroke than has previously been appreciated. The persistent nature of the risk even after cessation of smoking and the possible risk associated with passive exposure strengthens public health arguments against smoking.

Introduction

THE clinical picture of stroke can be produced by several pathophysiological mechanisms, the most important of which are atherothrombotic brain infarction, intracerebral haemorrhage, and subarachnoid haemorrhage. Before the development of computerised tomography (CT), the diagnosis of undifferentiated "stroke" was often contaminated by other causes of acute, focal neurological deficits, such as cerebral neoplasm, subdural haematoma, and cerebral abscess. Furthermore, the discrimination between pathophysiological subtypes was difficult. CT scanning, now established as a routine diagnostic procedure in most developed countries, provides an accurate and non-invasive means of subgrouping stroke types.

Risk factors for stroke have been identified in various epidemiological studies. Most were carried out before CT became available and attributed hypertension and ageing as the primary antecedents.^{1,2} Cigarette smoking, which is associated with atheroma generation elsewhere in the body, has been less consistently implicated as a major risk factor for stroke, although the latest studies have shown a more convincing association.³⁻⁷

Our aim was to examine the risk relation between cigarette smoking and subtypes of cerebral ischaemia whose pathogenesis is related to atherosclerotic change in major cranial and extracranial blood vessels. The hypothesis examined was that, without the possible diluting effect of cerebral haemorrhage and other non-thromboembolic causes of stroke, the stroke risk associated with cigarette smoking would be greater than that reported previously and that there may be subgroups with very high risk. We also took the opportunity to examine the effects of stopping smoking on any observed risk for cerebral ischaemia, together with any independent risk which may be attributable to smoking among other family members.

Patients and Methods

Nurse-interviews identified cases of acute cerebral ischaemia in four major hospitals serving the north-eastern region of Melbourne between 1985 and 1988. These hospitals manage most such cases in this area, the exception being the very old, who may be managed at home, in smaller private hospitals, or in nursing homes.

Patients were enrolled in the study if the clinical event was their first episode of cerebral ischaemia. Patients who died were included in the study by interview of closest relatives. The duration of cerebral ischaemia was defined to range from 24 h or less (transient ischaemic attack [TIA]) to a permanent deficit (cerebral infarction). There was no age restriction for study entry. CT scans were carried out on 98% of cases within 10 days of hospital admission. Those who did not receive CT scans were elderly, in a moribund state on admission, had cerebral ischaemia diagnosed on clinical grounds by the smattering nature of the progressive deficit, and died shortly afterwards. Patients in whom cerebral haemorrhage was shown on CT were excluded from the study.

Patients were asked to take part in a study of previous diet and lifestyle factors. A structured questionnaire was used to record information about personal characteristics, habits such as cigarette smoking, alcohol consumption, past dietary and exercise practices, and medical history (including that of treated hypertension). A

detailed list of current and past drugs was used to validate information about medical history. The section of the questionnaire about smoking sought information on current consumption, previous consumption in decades, type of cigarette, cigar, or pipe smoked, and degree of inhalation. The time since stopping smoking was recorded in periods of 2 years and then 5 years from the last cigarette to increase the reliability of recall. For the effects of passive smoking among other family members, patients were asked whether mother, father, or spouse smoked as many as 1 cigarette per day for as long as 1 year and, if so, what was the highest number smoked regularly for as long as 1 year. The latter was recorded as cigarettes per day in amounts of 10.

Controls were matched individually by age (± 5 years) and sex and were identified by knocking on doors in the same street (according to a strict protocol) until a household with a matching individual free of previous cerebrovascular disease was found. When an identified control was absent from the household, the interviewer returned on at least two further occasions to attempt contact. About 10% of identified controls refused to participate or could not be contacted and in these cases the next suitable neighbourhood control was chosen.

Each case and matching control were interviewed by the same nurse-interviewer. Only 1% of cases refused interview. In approximately 20% of cases communication was restricted and the closest available relative was interviewed; the closest available relative of the matched control was interviewed to avoid information bias. Most patients were interviewed while in hospital, but about 5% were interviewed at home because of rapid discharge from hospital.

The relative risk of cerebral ischaemia was estimated for subjects in various categories of smoking history, with the group who had never smoked as the reference category. Initially, unadjusted relative risks were calculated with paired data and then potentially confounding variables were controlled for by means of a conditional logistic regression model.⁸ Estimates of the relative risk associated with smoking were then made for the various categories of cerebral ischaemia with correction for hypertension and the small residual effect of age.

Definitions

Smoking categories.—We defined an ever smoker as a person who smoked at least 1 cigarette, cigar, or pipe per day for at least 3 months at some period during his or her life, a current smoker as a person smoking at least 1 cigarette, cigar, or pipe per day for the preceding 3 months, and an ex-smoker as a person who met the criteria for an ever smoker, but had not smoked for the preceding 3 months. The category never smoked included people who were not current smokers and who did not meet the criteria for ex-smoker or ever smoker.

Cerebral ischaemia was defined as acute onset of a focal neurological deficit in which CT scan excluded causes other than cerebral ischaemia; the duration of ischaemia could be 24 h or less (TIA), or longer than 24 h (cerebral infarction).

Lacunar syndrome was acute onset of one of the five recognised lacunar syndromes* (pure motor hemiplegia, ataxic hemiparesis, dysarthria clumsy hand syndrome, sensorimotor stroke, and pure sensory stroke) in which CT had excluded underlying cerebral haemorrhage. In many cases the site of infarction was identified on CT scan, but this was not an absolute requirement for classification as a lacunar syndrome.

Thromboembolic infarction was defined as acute onset of focal neurological deficit with documentation of the site of infarction on CT scan in either cerebral hemispheres or hind brain, in which the mechanism of infarction was attributed to large vessel extracranial or intracranial vascular disease.

Cardiac embolic cerebral infarction was the acute onset of a focal neurological deficit in which the site of infarction had been documented on CT scan in the presence of atrial fibrillation, myocardial infarction within the preceding 3 weeks, or cardiomyopathy. In some cases cerebral angiography or non-invasive studies of the extracranial circulation were done to help exclude carotid occlusive disease as a causal mechanism, but this was not an absolute requirement.

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TABLE I—AGE DISTRIBUTION OF 422 CASES AND CONTROLS

Age (yr)	Cases	Controls
<40	16	17
40-44	11	14
45-49	15	17
50-54	22	21
55-59	35	37
60-64	70	66
65-69	75	87
70-74	98	87
75-79	61	51
≥80	19	25

Cerebral infarct site or mechanism uncertain.—This group had acute onset of a focal neurological deficit in which the site of infarction or the mechanism of its genesis was unclear but causes other than vascular causes were excluded by CT scan.

Hypertension was defined as a history of hypertension documented by a medical practitioner or current use of antihypertensive drugs recorded at interview.

High cholesterol was defined as a plasma concentration of 5.5 mmol/l or greater.

Results

The 422 consecutive patients and their matched controls were of mean age 65 years (range 25-85 in patients, 20-87 in controls; table 1). There were 256 men and 166 women in each group. The relative risk (crude) of cerebral ischaemia for all factors which might have a confounding effect on smoking as a risk factor are shown in table II. These factors were controlled for by means of multiple logistic regression analysis.⁸ Smoking, hypertension, and a history of myocardial infarction were significant and independent risk factors, whereas alcohol consumption seemed to have a modest but significant protective effect. Since adjustment for all risk factors made little additional difference to the overall relative risks, adjustment for hypertension and age only was made for the rest of the analysis. Hence, the relative risk of cerebral ischaemia was 3.7 (95% confidence interval [CI] 2.3, 5.9) for current smokers and 2.0 (1.3, 3.1) for ex-smokers, both compared with those who had never smoked (adjusted for age and hypertension only). Both risks were significant ($\chi^2 = 30.0$ and 11.0 , respectively, each for 1 degree of freedom [df], $p < 0.001$ and $p < 0.01$). In women the risk for current compared with never smoking was 3.2 (1.6, 6.6); whereas in men the risk was slightly higher (3.8 [2.1, 7.0]); this difference was not significant ($\chi^2 = 0.1$ for 1 df, NS). Similarly, there was no difference between the sexes for ex-smoking risk (relative risk for men 1.8 [1.1, 3.1] and women 3.0 [1.3, 7.1]; $\chi^2 = 1.0$ for 1 df, NS).

The stroke risk was greatest in the group aged 55-64 years and the risk of stroke was significantly higher for current smokers under the age of 65 years than for those of 65 years or older (relative risk 6.8 [3.1, 15.0] vs 2.4 [1.2, 4.3]; $\chi^2 = 4.8$ for 1 df, $p < 0.05$). However, when the two groups in which smoking was not a risk factor (cardiac embolic and cerebral infarct with site or mechanism uncertain) were excluded from the analysis the difference was no longer apparent ($\chi^2 = 3.3$ for 1 df, NS). The mean ages of the cardiac embolic group (69 years) and the cerebral infarct, site or mechanism unknown group (68 years) were greater than that of the other groups (64 years).

There was a positive dose-response effect in that the risk of stroke among current smokers rose with the amount smoked. Two current smokers of the same age and hypertension status and whose daily consumption differed by one pack (20 cigarettes per day) were estimated to have a

TABLE II—CRUDE AND ADJUSTED RISKS OF CEREBRAL ISCHAEMIA FOR ALL FACTORS EXAMINED BY MULTIPLE LOGISTIC REGRESSION

	No (%) ^a		Estimated risk	
	Cases	Controls	Crude	Adjusted 95% CI [§]
Current smoker	135 (32%)	78 (18%)	3.2	3.6 (2.2, 5.9)
Ex-smoker	145 (34%)	137 (32%)	1.9	2.0 (1.3, 3.2)
Never smoked	142 (34%)	207 (49%)	1.0	1.0
Hypertension	281 (67%)	145 (34%)	4.2	4.7 (3.2, 6.8)
High cholesterol	45 (14%)	37 (11%)	1.6	1.3 (0.7, 2.5)
Myocardial infarction	84 (20%)	50 (12%)	1.9	1.6 (1.0, 2.5)
Alcohol consumption [†]	252 (68%)	274 (75%)	0.6	0.6 (0.4, 1.0)
Oral contraceptives [‡]	31 (19%)	39 (23%)	1.0	0.9 (0.4, 2.6)

^aOf subjects whose risk factor status was known.

[†]Yes or no.

[‡]Includes past as well as present use.

[§]Adjusted for all other risk factors.

risk differing by 2.1 (1.1, 3.8; χ^2 for linear trend = 6.7 for 1 df, $p < 0.01$).

The distribution of patients within each category of cerebral ischaemia with reference to smoking status is shown in table III. For current smokers, the greatest effect on stroke risk was for thromboembolic and lacunar stroke combined; the relative risk in this group was 5.7 (2.8, 12.0; $\chi^2 = 25.0$ for 1 df, $p < 0.001$). Patients with lacunar stroke alone had the highest relative risk associated with current smoking of all subgroups (infinite [3.0, infinity]); this risk was significantly higher than that for all other groups combined ($\chi^2 = 7.7$ for 2 df, $p < 0.05$), but only 10 matched pairs were available for analysis (the analysis method ignores pairs in which smoking status of case and control are the same) and this result should therefore be interpreted with caution. There was no risk associated with either current smoking or ex-smoking in the patients with cerebral infarction presumed to be due to cardiac emboli and patients in whom the site or mechanism of infarction was uncertain (table III). However, current smoking was a significant risk factor for TIAs (5.2 [2.1, 13.0]; $\chi^2 = 13.0$ for 1 df, $p < 0.001$).

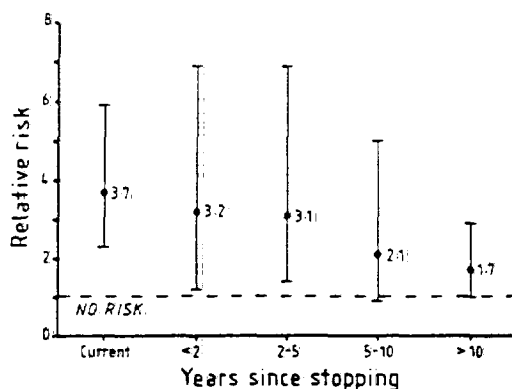
TABLE III—NUMBERS OF PATIENTS AND MATCHED CONTROLS IN EACH CLINICAL SUBGROUP OF CEREBRAL ISCHAEMIA WITH RESPECT TO SMOKING STATUS AND RELATIVE RISKS

Subgroup	No (%)			Relative risk of cerebral ischaemia* (95% CI)
	Current smokers	Ex-smokers	Never smoked	
TIA (n = 120)				
Cases	35 (29%)	53 (44%)	32 (27%)	
Controls	21 (18%)	42 (35%)	57 (47%)	5.2 (2.1, 13.0)
Thromboembolic (n = 163)				
Cases	59 (36%)	54 (33%)	50 (31%)	
Controls	36 (22%)	49 (30%)	78 (48%)	5.0 (2.3, 11.0)
Lacunar (n = 56)				
Cases	25 (45%)	13 (23%)	18 (32%)	
Controls	7 (13%)	19 (34%)	30 (54%)	Inf (3.0, Inf)
Cardiac embolic (n = 46)				
Cases	7 (15%)	14 (30%)	25 (54%)	
Controls	8 (17%)	15 (33%)	23 (50%)	0.4 (0.1, 1.8)
Site/mechanism uncertain (n = 37)				
Cases	9 (24%)	11 (30%)	17 (46%)	
Controls	6 (16%)	12 (32%)	19 (51%)	0.9 (0.2, 3.5)
Total				
Cases	135 (32%)	145 (34%)	142 (34%)	
Controls	78 (18%)	137 (32%)	207 (49%)	

*Current vs never smoked.

Inf = infinity.

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Effect of stopping smoking on relative risk of cerebral ischaemia.

Relative risk for each interval with 95% CI.

When the period since stopping smoking was divided into five intervals up to 10 years after stopping, a trend towards reduction in relative risk was seen (see accompanying figure). However, this trend was not significant ($\chi^2 = 0.5$ for 1 df, NS), and an appreciable risk was still apparent after 10 years.

The effect of passive smoking as a risk factor for cerebral ischaemia was assessed for each parent and for spouse. After control for the subjects' own smoking, hypertension, and the residual effect for age, smoking by the spouse increased the risk of stroke 1.7-fold (1.2, 2.6; $\chi^2 = 7.8$ for 1 df, $p < 0.01$), whereas smoking by a parent increased the risk 1.2-fold (0.8, 1.8; $\chi^2 = 1.2$ for 1 df, NS). The effect of a smoking spouse was slightly higher after exclusion of the two groups in which current smoking was not a risk factor (cardiac embolic and site or mechanism unknown). The relative risk for the remainder was 1.9 (1.2, 3.0). However, because we thought the observed effect of smoking by the spouse could be explained by current smokers with a smoking spouse tending to smoke more than those without, a further control for daily cigarette consumption of current smokers was introduced; this control did not change the estimates of relative risk for either parent or spouse. There appeared to be a positive dose-response effect in that the risk was increased by 1.3 per pack smoked by the spouse per day (χ^2 for trend = 4.8 for 1 df, $p < 0.05$). However, for never smokers only among the cases and matched controls, the relative risk associated with a smoking spouse was slightly lower (1.6 [0.6, 3.9]; $\chi^2 = 1.1$ for 1 df, NS), perhaps because only 88 matched pairs remained for analysis, and smoking by either parent was not a risk factor (relative risk 1.0, [0.5, 2.1]).

Discussion

The large number of cases and the high diagnostic precision by use of CT scanning in 98% of our cases has allowed us to extend the findings of previous studies in several important ways. First, in this "pure" sample of patients with cerebral ischaemia, not contaminated with other forms of "stroke", the relative risk associated with smoking was somewhat higher than that in other cohort⁴ and case-control^{1,7} studies. In four of those studies³⁻⁶ the use of CT scan was infrequent or not stated and the possibility that non-strokes as well as cerebral haemorrhages may have contaminated the sample is therefore higher. In the only

case-control study in which the clinical and CT entry criteria were similar to our own, outpatient medical clinic rather than community-based controls were used.⁷ Medical outpatient control groups are likely to be contaminated with smoking-related diseases, which may partly account for the lower relative risk found in that study. Second, in the two most common forms of stroke due to extracranial or intracranial vascular disease (lacunar and thromboembolic infarction) the relative risk associated with smoking was even higher, at five to six times that of those who had never smoked, and was of the same order of magnitude as treated hypertension as a risk factor. Third, the large number of cases in our study has enabled us to examine the nature of the relation between smoking and cerebral ischaemia in more detail than has been possible previously, particularly the effects of age and stopping smoking.

There are various mechanisms by which smoking may increase the risk of cerebral ischaemia. Smoking is known to increase platelet adhesiveness¹⁰ and fibrinogen levels and therefore blood viscosity.¹¹ Cerebral blood flow is reduced in chronic smokers,¹² perhaps because of the higher blood viscosity, but also vascular resistance may be greater because of the atherogenic properties of smoking.¹³

Our finding of an overall three to four times greater risk of cerebral ischaemia for smokers compared with non-smokers is similar to that reported for myocardial infarction,¹⁴ and higher than the two to three times greater risk previously reported for "stroke".^{3,7} The five to six fold increase in risk for lacunar and thromboembolic infarction is closer to that reported for peripheral vascular disease, in which one study reported an eight to nine fold increase in risk.¹⁵ In both myocardial infarction and peripheral vascular disease, the pathogenesis relates predominantly to atheromatous changes, so the similarly sized risks with pure forms of cerebral ischaemia would be expected.

Examination of other subgroups in our study showed that smoking is also a potent risk factor for TIAs. This finding confirms the general belief that cerebral ischaemia of brief or prolonged duration has a common underlying mechanism and hence similar risk factors. The reason for the lack of risk associated with smoking in the cardiac embolic group is uncertain, but a large proportion of this group had strokes secondary to atrial fibrillation, a cardiac disorder which is not associated with smoking as a risk factor.¹⁶ In the site and mechanism uncertain group the risk associated with smoking was also negligible. This finding emphasises the importance of a precise classification of stroke subtypes, since the group would otherwise contaminate the more clearly defined lacunar and thromboembolic groups. Although numbers were small (56 patients), the finding of a highly significant risk associated with smoking in the lacunar group compared with all other groups combined suggests that further study of the effects of smoking on small cerebral vessel disease may be useful. In the only other study to examine smoking as a risk factor for lacunar infarction,¹⁷ the relative risk was 2.3, but that study used hospital-based controls and current smokers were not analysed separately.

Given the positive dose-response effect of smoking on risk of cerebral ischaemia and the likelihood that atherogenesis may be at least partly the reason for this, it was somewhat surprising to find that patients younger than 65 years were at greater risk than those over 65 years. However, when the two groups in whom smoking was not a risk factor (cardiac embolic and site or mechanism uncertain groups) were excluded from the analysis, this differential in risk with age was lost. This finding is most likely due to the greater age of

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patients in whom stroke was due to atrial fibrillation in our study (69 years, compared with 64 years for the remainder), and the fact that smoking is not a risk factor for this rhythm disturbance.¹⁶ A significant risk differential with age for smoking and stroke has not been shown in previous studies, although in a meta-analysis of all known published studies on smoking and stroke, a significantly reduced risk with increasing age was shown.¹⁸ In view of our findings, and the fact that pathophysiological subgroups of stroke were not classified in most of the published studies, this effect in the meta-analysis may well be due to the unrecognised presence of elderly patients with atrial fibrillation as a stroke mechanism. In other words, there may not be an age effect in patients with cerebral infarction due to extracranial or intracranial vascular disease.

The persistence of the risk of cerebral ischaemia for at least 10 years after stopping smoking was surprising, since in the two cohort studies that addressed this question,^{16,17} the risk was found to return to that of never smokers within 2-5 years. However, in both those studies the number of patients who actually stopped smoking was much smaller and no distinction was made between cerebral haemorrhage and infarction in this part of the analysis. Since the known effects of smoking on platelet adhesiveness, fibrinogen levels, and blood viscosity are reversible within a short period, it seems likely that atherogenesis causes the persistence of risk as well as the major part of risk associated with current smoking.

The presence of a smoking spouse appeared to be an independent risk factor for cerebral ischaemia when all patients (smokers and non-smokers) were included in the analysis. A positive dose-response effect was observed for this risk with the number of cigarettes smoked by the spouse and the risk was more evident when cerebral ischaemia due only to extracranial or intracranial vascular disease was analysed. However, for non-smokers alone, there was a similar but non-significant increase in risk perhaps because of the restriction to fewer matched pairs in the analysis. Considering these two analytical methods together, it appears likely that passive smoking has a small effect. Since passive smoking is now such an important social issue, and has been shown to be a risk factor for non-smokers for other diseases¹⁹ our preliminary findings on this subject certainly warrant further study.

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PERCUTANEOUS CORONARY EXCIMER LASER ANGIOPLASTY: INITIAL CLINICAL RESULTS

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Summary A novel 1.3 mm diameter laser catheter, consisting of 20 concentric 100 µm quartz fibres around a central lumen for a 0.35 mm flexible guide wire, was used to ablate atherosclerotic tissue in thirty patients with coronary artery disease. The laser catheter was coupled to an excimer laser delivering energy at a wavelength of 308 nm and a pulsewidth of 60 ns. The primary success rate was 90% (27 of 30 lesions). The mean (SD) percentage stenosis fell from 85 (15)% to 41 (19)% after laser ablation. In ten patients the lumen diameter after laser angioplasty was considered sufficient, but subsequent balloon angioplasty was carried out for the other twenty patients. Failure to pass the lesion was caused by vessel kinking in two patients and a total occlusion in one patient. No complications directly attributable to laser ablation, such as vessel wall perforation, occurred; one dissection occurred but had no clinical sequelae. There was one early reocclusion and death in a patient with triple vessel disease and unstable angina, probably as a result of plaque rupture after balloon angioplasty. These results are encouraging and justify further clinical investigations.

Introduction

PERCUTANEOUS transluminal coronary angioplasty has been widely accepted as treatment for coronary artery disease.^{1,2} Restenosis, however, greatly limits the clinical efficacy of balloon angioplasty.^{3,5} The use of laser energy transmitted through flexible fibreoptic fibres may be a possible adjunct or alternative to conventional angioplasty, because it removes atherosclerotic tissue or thrombus by vaporisation rather than by stretching and fracturing of the stenosis as in balloon angioplasty.^{6,7} In-vivo studies have shown not only greater efficacy of laser-heated probes but

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MATSUSHITA, M., SHIONOYA, S. AND MATSUMOTO, T., "URINARY COTININE MEASUREMENT IN PATIENTS WITH BUERGER'S DISEASE -- EFFECTS OF ACTIVE AND PASSIVE SMOKING ON THE DISEASE PROCESS," J VASC SURG 14(1): 53-58, 1991.

Buerger's disease is an inflammatory condition leading to arterial occlusion in the peripheral vascular system. It has been reported to be strongly associated statistically with cigarette smoking. Matsushita, et al. studied 40 Buerger's disease patients, all of whom had a smoking history. Using urinary cotinine levels as a marker, these patients were classified either as smokers, as "passive smokers" (i.e., as nonsmokers exposed to ETS) or as nonsmokers not exposed to ETS.

When the progression or "aggravation" of the disease was examined retrospectively, it was reported to have worsened in seven of 10 of the smokers, in none of the nine "passive smokers" and in four of the 21 non-ETS-exposed nonsmokers. Among this last group, three of the four admitted to "active" smoking and the fourth reported exposure to ETS in the workplace.

Statistical tests revealed that the course of Buerger's disease had significantly worsened in the smokers, relative to the other two groups. However, there was no statistically significant difference between the "passive smoking" and non-ETS-exposed group. Based on these data, the authors concluded that their results confirmed the relationship of "active" smoking with Buerger's

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disease, but that the "effects of passive smoking on the disease process were still inconclusive."

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Urinary cotinine measurement in patients with Buerger's disease—Effects of active and passive smoking on the disease process

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Although Buerger's disease is known to be closely related to smoking, no objective analysis of the smoke-associated problems has been performed. In this study, cotinine, the major metabolite of nicotine, was used as a sensitive marker to measure levels of active smoking and the exposure of nonsmokers to tobacco smoke because it has a relatively long half-life and because cotinine levels can be determined by noninvasive means in urine. According to urinary cotinine levels, 40 patients with Buerger's disease were classified as (1) smokers: those with urinary cotinine levels above 50 ng/mg creatinine; (2) passive smokers: those with levels between 10 and 50 ng/mg creatinine; and (3) nonsmokers who did not experience noticeable passive smoking: those with levels below 10 ng/mg creatinine. There were 10 smokers, 9 passive smokers, and 21 nonsmokers. The course of the disease, after the initial treatment at our hospital, was studied retrospectively. Seven of the 10 smokers, none of the 9 passive smokers, and 4 of the 21 nonsmokers experienced aggravation of the disease. Of the four nonsmokers who experienced aggravation, three had still been smokers and one had been exposed to tobacco smoke in the workplace at the time of relapse. There was a significant difference in the aggravation rate between the smokers' group and the other two groups. Among the smokers, the seven patients whose conditions worsened showed significantly higher cotinine levels than the three remaining patients who were in the stage of remission. The conclusions were: (1) a very close relation between active smoking and the course of Buerger's disease was established, and (2) effects of passive smoking on the disease process were still inconclusive. (*J Vasc Surg* 1991;14:53-8.)

Buerger's disease is characterized by peripheral arterial occlusion of the extremities most frequently in young adult male smokers.^{1,2} In general, all patients with Buerger's disease have a history of smoking, and smoking is also known to be closely related to exacerbations of the disease.^{1,3} The outlook in regard to the effects on the limbs of a patient with Buerger's disease is favorable if he stops smoking, but the disease gets progressively worse if he continues to smoke.^{3,4}

However, we have occasionally found that the disease recurred in patients who stated that they had abstained from smoking. Many of them may have been lying about their smoking habits: some were

deemed to have denied themselves the pleasure of smoking but had been exposed to tobacco smoke in the home and workplace. Because there is no objective test to evaluate smoking, previous studies have had to depend on patients' testimony of smoking habits. An objective method of evaluation of the degree of active and passive smoking is necessary to elucidate the relationship between smoking and Buerger's disease.

By measuring urinary concentration of cotinine, the major metabolite of nicotine, we found a correlation between smoking and the natural course of Buerger's disease in retrospective study.

PATIENTS AND METHODS

Urine samples were collected for measurement of nicotine and cotinine levels from 50 volunteers (23 smokers and 27 nonsmokers) without noticeable passive smoking and whose statements of smoking histories were regarded as reliable. The time pattern of nicotine and cotinine excretion was studied to judge whether alkaloid is suitable as the marker for

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smoking from the standpoint of the half-life of cotinine in the human body. For this purpose, urinary nicotine and cotinine levels of a healthy nonsmoker (one of the authors) were measured after he had smoked one cigarette and after he had been placed in a passive smoking environment. For our passive smoking experiment, the subject was placed in an airtight room (19.1 m^3) and exposed to side-stream tobacco smoke from a total of 40 cigarettes for 3 hours.

Urine samples from 40 patients with Buerger's disease were collected (one for each case) when the patients came to our clinic. Each patient's statement about current smoking status and involuntary exposure to smoking was requested at each visit. Our clinical criteria for the diagnosis of Buerger's disease are: (1) history of smoking; (2) onset before the age of 50 years; (3) infrapopliteal arterial occlusive disease; (4) either upper-limb involvement or phlebitis migrans; and (5) absence of atherosclerotic risk factors other than smoking. The clinical diagnosis of Buerger's disease was made when all five requirements were met.^{1,3} Infrapopliteal obstruction was confirmed by arteriography in each case, and arteriographic findings such as tapering or abrupt occlusion, corkscrew or rootlike appearance of collaterals, and corrugated appearance served as supporting evidence. All of the patients had a history of smoking before the onset of the disease. At onset, the age of these 40 patients ranged from 26 to 49 years (mean, 37 years). There were 38 men and 2 women. All 40 patients had been treated in our institution for more than 1 year, and their case histories were reviewed retrospectively. The initial treatments of these patients were bypass grafting and sympathectomy in 2; bypass grafting in 4; sympathectomy in 24; and medical treatment only in 10. The follow-up period ranged from 1 to 22 years, with a mean of 8.3 years. In case of recurrence of pain at rest, ischemic ulceration, or graft failure (except early failure, less than 30 days), which were confirmed by follow-up surveillance, the patient was considered clinically to have "aggravation of the disease."

Urinary nicotine and cotinine levels were determined by high-performance liquid chromatography (HPLC) according to Mizobuchi's method⁵ with some modifications. We changed the extraction procedures in order to assess very low levels of these alkaloids. Urine samples were stored at -20°C until analysis. Ten milliliters of urine was centrifuged. After the addition of 4 gm sodium chloride, 0.1 ml 25% ammonium hydroxide, and 2 ml chloroform, the urine samples were shaken for 10 minutes and

centrifuged at 12,000 rpm for 10 minutes. The chloroform layer was collected and then shaken with 5 ml of 0.1 N hydrochloric acid for 10 minutes and centrifuged at 12,000 rpm for 10 minutes. The resulting aqueous layer was shaken with 2 gm sodium hydrochloride, 0.2 ml ammonium hydrochloride, and 1 ml chloroform, and then centrifuged at 12,000 rpm. Fifty microliters of this chloroform layer was used for the HPLC. Average total recoveries were 98% for nicotine and 85% for cotinine. The detection limits of nicotine and cotinine were 2 ng/ml and 3 ng/ml, respectively. Urinary nicotine and cotinine values were normalized by creatinine excretion and expressed as nanograms per milligram of creatinine.

Statistical significance was assessed by Student's *t* test or chi-square analysis, and the results were considered significant at $p < 0.05$.

RESULTS

For the healthy control subjects, urinary nicotine levels were $576 \pm 474 \text{ ng/mg creatinine}$ (mean value \pm standard deviation) in the smokers, and $5.2 \pm 3.8 \text{ ng/mg creatinine}$ in the nonsmokers who did not have perceptible involuntary exposure to tobacco smoke ($p < 0.01$). Urinary cotinine levels for these two groups were also significantly different ($859 \pm 814 \text{ ng/mg creatinine}$ in the smokers vs $5.6 \pm 2.3 \text{ ng/mg creatinine}$ in the nonsmokers, $p < 0.01$). Urinary cotinine levels discriminated between the smokers and the nonsmokers more distinctly than nicotine levels. Therefore those with urinary cotinine levels above 50 ng/mg creatinine may be regarded as smokers (Fig. 1). In smokers, urinary excretion of cotinine roughly correlated to self-reported cigarette consumption (Fig. 2). Fig. 3 shows urinary nicotine and cotinine levels in a healthy nonsmoker after he had smoked one cigarette and after he had been exposed to side-stream smoke. Urinary cotinine elevation after active smoking lasted for 60 hours. The urinary cotinine level after passive smoking was lower compared with the level after active smoking, but it showed the same rise and fall as the level after active smoking. The disappearance of nicotine from the urine was faster than that of cotinine. Because of this, only the urinary cotinine level was used for studies on the patients.

Fig. 4 shows the urinary cotinine levels in patients with Buerger's disease. All three patients who confessed themselves to be current smokers had cotinine levels that were higher than 50 ng/mg creatinine. Of the 37 patients who asserted that they were not active smokers, seven (19%) had cotinine levels above 50 ng/mg creatinine. According to our definition, these

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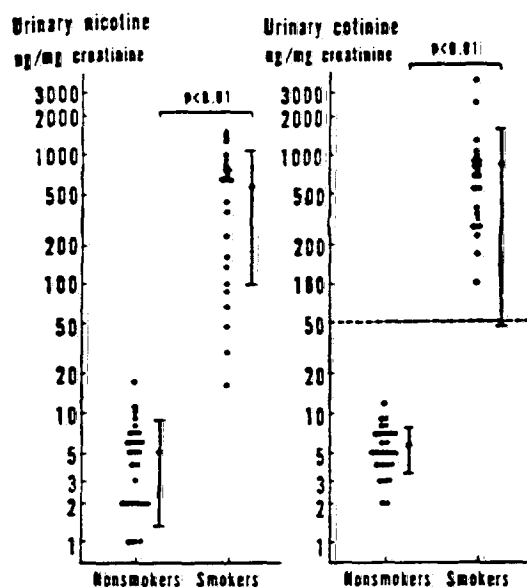


Fig. 1. Urinary nicotine levels (left) and cotinine levels (right) of nonsmokers and smokers, in healthy control subjects. There were significant differences between the two groups ($p < 0.01$). Cotinine levels discriminate between smokers and nonsmokers more distinctly than nicotine levels do.

seven patients were considered active smokers, whereas the other 30 patients were regarded as exsmokers. The 30 exsmokers were then divided into two groups, on the grounds of self-reported involuntary exposure to smoking. Urinary cotinine levels were 10.2 ± 4.2 ng/mg creatinine in those who were involuntarily exposed to smoking and 6.1 ± 3.5 ng/mg creatinine in those who were not exposed ($p < 0.01$) (Fig. 5). On the basis of these results, we decided that for this study, those with urinary cotinine levels between 10 and 50 ng/mg creatinine would be identified as nonsmokers with noticeable passive smoking (passive smokers) and those with levels below 10 ng/mg creatinine would be identified as nonsmokers without perceptible passive smoking (Fig. 5).

The 40 patients were classified into three groups: (1) those with urinary cotinine levels above 50 ng/mg creatinine (active smokers), (2) those with cotinine levels between 10 and 50 ng/mg creatinine (passive smokers), and (3) those with cotinine levels below 10 ng/mg creatinine (nonsmokers without noticeable passive smoking). Eventually, 10 patients were classified as active smokers, 9 as passive smokers, and 21 as nonsmokers. The disease worsened in 7 (70%) of

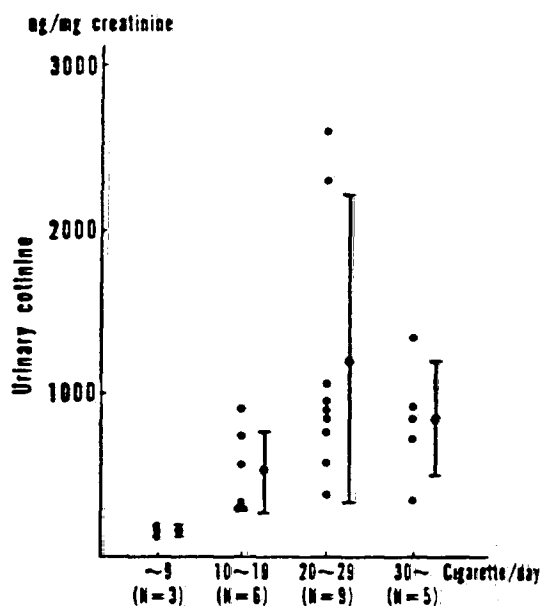


Fig. 2. Urinary cotinine levels in smokers. Smokers were classified into four groups on the basis of self-reported cigarette consumption. Urinary cotinine levels roughly correlated to daily cigarette consumption.

the 10 smokers; in none (0%) of the 9 passive smokers; and in 4 (19%) of the 21 nonsmokers. There were significant differences in the rate of the aggravation of the disease between the smokers and the passive smokers ($p < 0.01$) and between the smokers and the nonsmokers ($p < 0.01$). However, no significant differences in the rate of aggravation were found between the passive smokers and the nonsmokers (Fig. 6). Of the four exsmokers who experienced worsening of the disease, three admitted that they had still been active smokers at that time. The other one stated that he had been involuntarily exposed to noticeable smoking in the workplace all day at the time of recurrence. This patient had sympathectomy and bypass operation of the left leg for the initial treatment. Four years later, femorocrural bypass grafting in the right leg was necessary because of right popliteal artery occlusion that was a result of a skip lesion. Thereafter, however, he has kept away from tobacco smoke in the workplace and he has been doing well for 2 years (Fig. 6). Among the 10 current smokers, the mean cotinine level for the seven patients who had aggravation of the disease was significantly higher than the level for the three patients who did not experience relapses (1208 ± 734 ng/mg creatinine vs 147 ± 79 ng/mg creatinine, $p < 0.05$).

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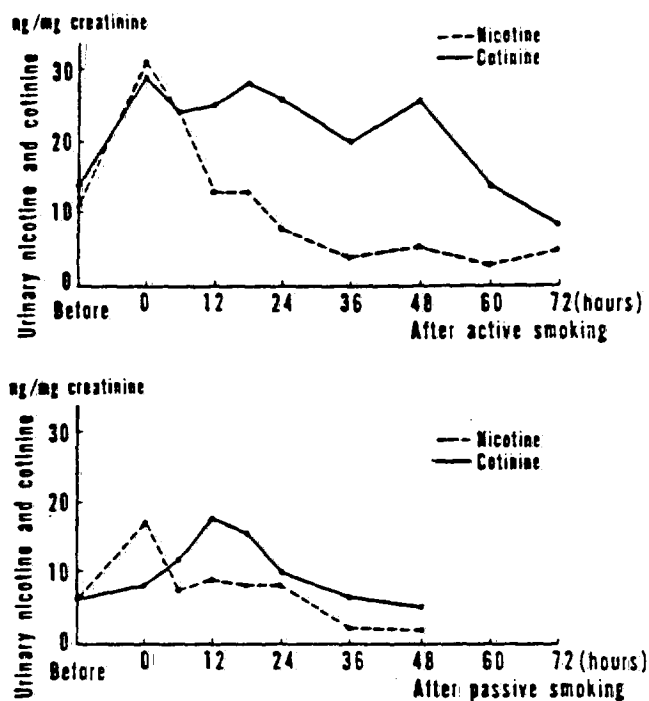


Fig. 3. Urinary nicotine (broken line) and cotinine (solid line) excretion over time. After active smoking (above), and after high involuntary exposure to smoke (below), in a healthy nonsmoker. Cotinine levels decreased more slowly than nicotine levels did.

DISCUSSION

Carboxyhemoglobin or nicotine concentrations have been used as indicators of smoking.^{6,7} In vascular surgery, carboxyhemoglobin has been used to determine smoking habits of patients who had arterial reconstructive operations,^{8,9} and Wiseman et al.⁹ reported that the median concentration of carboxyhemoglobin was significantly higher in those patients whose grafts had failed than in those whose grafts were patent. However, blood carboxyhemoglobin concentrations have not proved to be markers specific to smoking, and nicotine measurements have been regarded as providing more accurate assessments.¹⁰ Recently, cotinine has been considered a more sensitive marker of smoking because it has a much longer plasma half-life than nicotine does (about 30 hours vs about 30 minutes).^{11,12} In this study, urinary cotinine levels clearly discriminated between smokers and nonsmokers. By measurement of cotinine levels, 10 patients were identified as active smokers, although seven of them claimed to have quit smoking. Of these 10 active smokers, seven experienced aggravation, and there was a significant difference in the rate of aggravation between active smokers and exsmokers. It was confirmed that active

smoking was very closely related to recurrences of Buerger's disease. Three former smokers, however, experienced worsening of the disease even though their urinary cotinine level remained within a nonsmoker's or a passive smoker's range. Since the urinary cotinine elevation after smoking lasted for only 60 hours, our assessments of smoking were limited to a very short period. Past smoking habits cannot be estimated by ill-timed measurement of cotinine, a short-term marker, when patients have abstained from smoking. Serial examination of urinary cotinine levels should be performed to solve this problem.

Because the number of cigarettes smoked roughly correlated with the urinary cotinine level,^{13,14} this level may reflect the intensity of smoking. However, there was considerable variation in cotinine excretion among subjects who smoked approximately the same number of cigarettes. These variations were assumed to be caused by differences in nicotine content per cigarette and in the manner of smoking (inhaling or puffing, frequency, length of cigarettes smoked).^{12,14} In this study, among the patients who continued to smoke, those who experienced aggravation of the disease had significantly higher cotinine levels than

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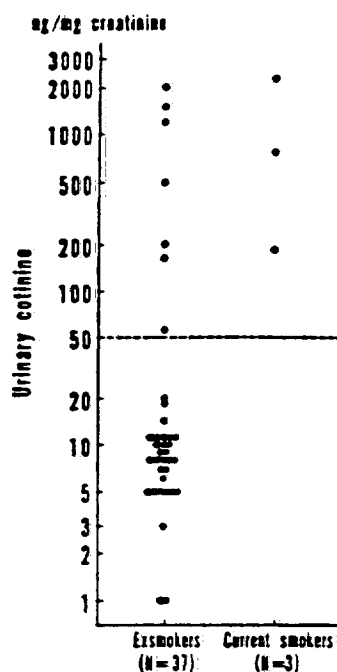


Fig. 4. Urinary cotinine levels. Patients were divided into two groups according to their statements about their smoking habits. Regardless of their claims, they were classified as smokers if they had urinary cotinine levels above 50 ng/mg creatinine.

those who were in remission. However, even among those who experienced aggravation, the urinary cotinine levels varied widely. It seems impossible to predict which patient will become worse, judging from the number of cigarettes that were smoked.

Recent studies have indicated that involuntary exposure to smoking may be as harmful as active smoking.¹⁵ Sinzinger and Kefalides¹⁶ reported that passive smoking reduced platelet sensitivity to anti-aggregatory prostaglandins (E_1 , I_2 , D_2), and the reduction in sensitivity was much more severe in nonsmokers than in smokers. Passive smoking might exert a poor influence on the cardiovascular system for nonsmokers. In this study, the influence of involuntary exposure to smoking on Buerger's disease was studied by measurement of urinary cotinine levels, but no significant relationship between involuntary exposure to smoking and recurrence of the disease was found. However, there was one patient who had aggravation of the disease, who testified to have abandoned smoking habits, and this person had the urinary cotinine level of a nonsmoker. Because he had been involuntarily exposed to noticeable smoking at the time of worsening of the disease and is not

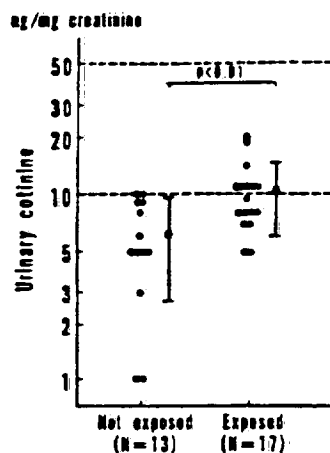


Fig. 5. Urinary cotinine levels of nonsmokers without involuntary exposure to smoking and nonsmokers with involuntary exposure to smoking. There was a significant difference between the two groups ($p < 0.01$).

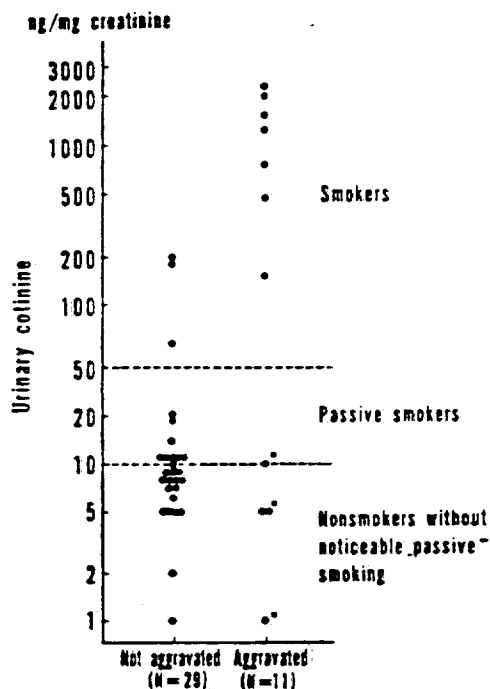


Fig. 6. Urinary cotinine levels and the course of Buerger's disease. There were significant differences in aggravation between the smokers' group and the other two groups, but no significant differences were found between passive smokers and nonsmokers without noticeable passive smoking. Three (asterisks) of the four nonsmokers with aggravated conditions stated that they had been smoking at the time of worsening of the disease.

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exposed to tobacco smoke now, the worsening of his disease may be associated with the past involuntary exposure to smoking. The incorrect timing of urinary cotinine measurement may explain why no significant relationship was found between passive smoking and the worsening of the disease in this study. A cooperative epidemiologic and clinical study that is based on the long-term and timely evaluation of effects on health of involuntary exposure to smoking may provide the evidence to support the hypothesis that passive smoking can influence the occurrence of Buerger's disease and the worsening of the disease process.

In conclusion, cotinine is a sensitive but short-term marker of smoking. Smoking tobacco was very closely related to the course of Buerger's disease, but no significant correlation between passive smoking and the disease process has been found yet.

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AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING

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The purpose of this paper is to estimate the number of adult deaths per year in the United States from passive smoking. The epidemiological literature on passive smoking and adult mortality and cancer and heart morbidity is reviewed. Combined relative risks for lung cancer, cancers other than lung, and heart disease are calculated for each sex and disease category. These data along with estimates of nonsmoker death rates and populations exposed allow calculation of annual deaths in each category. Reduced relative risk and reduced exposure at older ages are taken into account as well as a correction for possible misclassification of smokers as nonsmokers and exposed nonsmokers as nonexposed. Altogether 46,000 deaths per year are calculated consisting of lung cancer (3000) other cancer (11,000) and heart disease (32,000). Reasons why such high estimates for other cancer and heart disease may be possible are explored. It is concluded that exposure to environmental tobacco smoke can have adverse long term health effects that are more serious than previously thought.

Introduction

Several attempts have been made to estimate U.S. adult mortality from passive smoking. For example, Repace and Lowrey (1985) estimated the lung cancer deaths to be about 5000 per year. Fong (1982) estimated total mortality at 10,000 to 50,000. Russell *et al.* (1986) estimated total U.S. mortality at more than 4000. The present estimate is based on epidemiological evidence currently available on lung cancer, cancers other than lung, and heart disease.

The Surgeon General of the United States (USSG, 1986) and the U.S. National Academy of Sciences (NRC, 1986) have issued reports stating that passive smoking can cause lung cancer. In the National Academy report the relative risks from the various lung cancer studies were combined into an overall relative risk using a procedure somewhat similar to that which is used in this work. The Academy report then projects that about 20% of the 12,000 U.S. lung cancer deaths per year among never smokers is due to passive smoking. This is reasonably close to the 3000 per year projected here for never smokers plus exsmokers. The methods used in the National Academy report are further detailed in Wald *et al.* (1986). Blot and Fraumeni (1986) have also presented an overview of studies of lung cancer and passive smoking. They use a method

of combining the relative risks from various studies essentially identical to that used here. Thus, the procedure of combining relative risks from various passive smoking studies to obtain overall relative risks and tighter confidence intervals is now well established by authorities in the field. Also, the method used here to calculate annual deaths from the relative risks appears to be validated by the National Academy results for lung cancer. However, both the Surgeon General's task force and that of the National Academy felt that the data, as of 1986, on cancers other than lung and on heart disease were still too meager to allow calculation of reliable overall risks.

Since 1985 considerably new epidemiological information has become available, particularly on heart disease. This new information is reviewed and combined with the old data to calculate updated relative risks, overall confidence limits, and estimated annual U.S. deaths from passive smoking and the three main diseases, namely, lung cancer, cancers other than lung, and ischemic heart disease. The total particulate matter dose retained by passive smokers is too low to account for the health effects of passive smoking if one starts with the health effects exhibited by direct smokers and ratios down from the dose retained by them. Reasons why such a discrepancy might occur are explored.

Methods

Studies to be considered in the analyses were obtained originally from the literature searches of the U.S. Office on Smoking and Health (OSH, 1979-85). More recently, studies have come to light primarily through personal contact with workers in the passive smoking field. Criteria for admitting data to the analysis are:

1. Studies on the association of passive smoking with adult mortality or morbidity from lung cancer, other cancer or ischemic heart disease were included. All cause data were not used because essentially no male data are available. The female data, if calculated, yield overall results that are in the same range as the results derived from the three main diseases (see Appendix B). Emphysema is not included because the nonsmoker death rate is so low that less than 1% of deaths from passive smoking would be predicted from this source (see Appendix B).
2. Retrospective studies should have controls.
3. Observations should be based on spouse exposure or on general exposure of more than 10 years duration. The diseases under study are known to have long induction periods, and it is assumed that most married people old enough to die of passive smoking would have been exposed 20 years or more.
4. Enough data should be available from the study to allow calculation of a weighting factor for combining the relative risks.

Two risk models were used and a third was considered. The primary model used combined relative risks from the various studies that pertained to a given sex and disease and assumed that the combined relative risk was constant with age, although variation with age of the underlying never-smoker death rate and the fraction of the population exposed were included. In the secondary risk model the combined relative risk was also allowed to vary with age. These models were suggested in part by the considerations in James Robins' Appendix D in the National Academy report (NRC, 1986). The third risk model was based on the rate difference between the death rates for exposed and nonexposed populations. A detailed analysis of this model for heart disease in women was carried out (see Appendix C). It was concluded that the relative risk models were much superior to the rate difference model when combining data across different cultures as is the case here where some of the studies are from the orient.

Wherever a study showed both a crude relative risk or odds ratio and an adjusted ratio, the adjusted ratio was used. To obtain a combined relative risk a method similar to that of Blot and Fraumeni (1986) was used. Case control studies were aggregated using Program 2 of Rothman and Boice (1982). Cohort studies were aggregated using Program 7. A combined relative risk for

the two aggregates was obtained using:

$$R_{cb} = \exp \frac{w_{co} \ln R_{co} + w_{cc} \ln R_{cc}}{w_{co} + w_{cc}} \quad (1)$$

where R_{cb} , R_{co} , and R_{cc} are the relative risks for the combined total, the cohort studies, and the case control studies, respectively, and w_{co} and w_{cc} are the weights for the cohort and case control studies, respectively, which are the inverse of the respective variances. Variance is taken as the square of the standard deviation which is equal to $\ln R/\chi$, so the weight, $w = (\chi/\ln R)^2$. The source of these equations is Rothman (1986). Confidence intervals were calculated from a combined $\chi^2 = w_{cb}^2 \ln R_{cb}$. For some studies it was necessary to calculate a χ^2 from the confidence limits in order to calculate a weight since no other data were available. These data were then combined with the rest using Eq. (1). Ages of death from 35 and up were used and should include essentially all adult deaths from passive smoking. In some studies morbidity relative risks were reported whereas our interest is in mortality. The morbidity relative risks were accepted as surrogates for mortality relative risks because, for cancer, the survival rates for exposed and nonexposed cases appeared to be similar while, for heart disease, incidence relative risks, if anything, are lower than mortality relative risks (Svensden *et al.*, 1987).

The 1985 smoking status for U.S. residents in 5 year age increments was obtained from the National Center for Health Statistics. Nonsmokers were equated to never smokers plus exsmokers. The fractions of never smokers living with ever smokers (24% for males and 60% for females), all of whom were considered to be exposed, were obtained from controls of the U.S. based studies for all three diseases. These fractions were assumed to hold also for nonsmokers (never plus ex). The fractions of all nonsmokers exposed as nonsmokers living with nonsmokers, but still exposed at home or at work (37% for males and 16% for females), were obtained from Friedman *et al.* (1983). These fractions were assumed to hold for nonsmokers living with never smokers. By adding the two fractions the total nonsmoker exposure of 61% for males and 76% for females was obtained. These overall exposure fractions are known to be higher at younger ages and lower at older ages. The data of Friedman *et al.* (1983) were used to develop smoothed values of fraction exposed 10 years earlier (midpoint of a 20 year exposure) for each sex and 5 year age interval normalized to 61% for males and 76% for females. By multiplying each population element by each fraction exposed element, the exposed population by sex and 5 year age interval could be determined.

Death rates for never smokers for lung cancer by sex and 5 year intervals were drawn from Garfinkel (1981).

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and smoothed using a semi-log plot against age. For cancers other than lung for females a semi-log plot of 1984 age specific death rates for ages 35+ was developed for malignant neoplasms less malignant respiratory neoplasms from the data of the National Center for Health Statistics (1986). Then, a parallel plot was developed using as reference points the never-smoker data of Hammond (1966) for ages 45-64 and 65-79 to yield never-smoker rates for ages 35+ for each 5 year age interval. For heart disease never smoker death rates by sex and 5 year age intervals for 1963 were developed from the appendix tables in Hammond (1966). These were reduced to 1984 equivalent rates (with the reduction factors corrected for the effects of smoking) by a technique similar to that used by the U.S. Office of Technology Assessment (OTA, 1985). Semi-log graphs were used to estimate never smoker death rates by 5 year age intervals for the entire age range (see Appendix A, Table A3).

The excess death rate for never smokers for passive smoking (D_{ps}) for each sex, disease and 5 year age range was calculated from the never smoker death rates (D_n) using the formula:

$$D_{ps} = D_n(R - 1)/(F_p(R - 1) + 1) \quad (2)$$

where F_p is the fraction of the population that is exposed and R is the combined relative risk. This excess death rate was assumed to apply to all nonsmokers. Deaths were then calculated by multiplying the passive smoking excess death rate by the exposed population for each sex and 5 year age interval, and summed. For those calculations where the relative risk was assumed to have varied with age, the excess death rates for passive smoking were recalculated from the age specific relative risks for each 5 year age interval. Additional calculations were carried out to show the effects of bias including those from misclassification of smokers as nonsmokers and exposed nonsmokers as unexposed, using a method similar to that of Wald *et al.* (1986).

Results

Relative risks

The results for passive smoking relative risk for females for lung cancer are shown in Table 1. The three cohort studies are listed first and show a combined relative risk for all exposures including exposures to ex-smokers of 1.34. At the time the analysis was made there were fourteen acceptable case control studies with a combined relative risk of 1.50. The overall combined relative risk, based on 1,174 cases, is 1.44 with 95% confidence limits of 1.3-1.7. The male lung cancer observed relative risks are shown in Table 2. There are now nine studies with 144 total cases. The overall combined relative risk is 2.1 with 95% confidence limits of

1.3-3.2. Data excluded from Tables 1 and 2 along with the reasons were the following: Chan *et al.* (1979), current exposure only; Knott *et al.* (1983), no controls; Kabat and Wynder (1984) nonspouse data, current exposure only; Buffler *et al.* (1984), 0-32 year data, not a minimum of 10 years exposure. A paper by Dalager *et al.* (1986) describes a pooling of data from Correa *et al.* (1983), Buffler *et al.* (1984) and a study of males in New Jersey. They observed an adjusted odds ratio for spouse exposure of 1.47, but since Correa *et al.* (1983), and Buffler *et al.* (1984), were already included in Tables 1 and 2 and since the New Jersey data were not available separately, it was decided to omit the Dalager *et al.* (1986) study from this analysis. Also, available were abstracts of two recent papers, Geng *et al.* (1987) from China with a relative risk of 2.2 and Inoue and Hirayama (1987) from Japan with a relative risk of 2.3, both for females. Also W. K. Lam (1985), in a thesis from the University of Hong Kong that is quoted in Lam *et al.* (1987) found a relative risk of 2.0 for adenocarcinoma among females. These inputs arrived too late to be included in the analysis.

The data of Hirayama (1984a) on female lung cancer are sufficiently detailed to indicate a declining relative risk with age from 1.87 at approximately age 50 to 1.43 at approximately age 75. These data were used to develop a second death calculation assuming a declining relative risk, but still normalized to 1.44. However, Hirayama's data show no such decline in passive smoking relative risk with age for males. Instead, the trend appears to rise with age, so no secondary calculation was made.

There are now five studies relating passive smoking to total cancer or cancer other than lung in females. The individual and combined relative risks for females are shown in Table 3. The total combined relative risk is 1.16. The total cases, 2,933, are two and one-half times the total cases for female lung cancer (Table 1) although 2,505 are concentrated in the large Hirayama (1984a) study. This is a large data base. The total combined chi square is 11 compared to 27 for female lung cancer.

The two largest of the female studies, Hirayama (1984a) and Sandler *et al.* (1985), cover different age of death ranges. Hirayama covers 50 to 80+ while Sandler *et al.* cover <30 to 59. The two studies taken together would indicate a rather sharp decline in relative risk with age from about 3.5 at age 40 to about 1.04 at age 80. The high relative risks at the younger ages may be due to premenopausal breast cancer (see Sandler *et al.*, 1986). Two calculations of U.S. female deaths from passive smoking and other cancers were made, one using the 1.16 relative risk from Table 3 at all ages and one using the declining relative risks.

Gillis *et al.* (1984), Sandler *et al.* (1985), and Reynolds (private communication) also report on other can-

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Table 1. Female relative risks for lung cancer from passive smoking.

	Locale	Total Cases	Highest Exposure		All Exposures			Mantel Trend
			RR	2-tail p	RR	95 % C.L.	1-tail p	
Cohort Studies:								
Hirayama (1984a)	Japan	200	1.9	0.002	1.6	1.1-2.2	0.002	
Garfinkel (1981)	United States	153	1.1	—	1.2	0.8-1.6	—	
Gillis <i>et al.</i> (1984)	Scotland	8	—	—	1.1	0.2-5.6	—	
Combined Cohort		361			1.34	1.1-1.7		
Case Control Studies:								
Trichopoulos <i>et al.</i> (1983)	Greece	77	2.6	0.19	2.1	1.2-3.6	0.005	
Correa <i>et al.</i> (1983)	Louisiana	22	3.5	0.02	2.1	0.8-5.2	—	
Buffler <i>et al.</i> (1984)	Texas	27*	—	—	0.9	0.4-2.3	—	
Kabat and Wynder (1984)	United States	24	—	—	0.8	0.3-2.5	—	
Sandler <i>et al.</i> (1985)	North Carolina	2	—	—	inf	—	—	
Garfinkel <i>et al.</i> (1985)	United States	116	2.0	0.05	1.3	0.8-1.9	0.025	
Wu <i>et al.</i> (1985)	California	28*	—	—	1.2	0.5-3.3	—	
Lee <i>et al.</i> (1986)	United Kingdom	32	—	—	1.0	0.4-2.7	—	
Akiba <i>et al.</i> (1986)	Japan	94	2.1	—	1.5	0.9-2.6	0.06	
Koo <i>et al.</i> (1987)	Hong Kong	86	1.2	—	1.6	0.9-3.1	—	
Pershagen <i>et al.</i> (1987)	Sweden	67	3.2	—	1.2	0.7-2.1	0.12	
Humble <i>et al.</i> (1987)	New Mexico	20	1.2	—	2.3	0.9-6.6	—	
Brownson <i>et al.</i> (1987)	Colorado	19	—	—	1.7	0.4-3.0	—	
Lam <i>et al.</i> (1987)	Hong Kong	199	—	—	1.65	1.2-2.4	—	
Combined Case Control		813			1.50		1.3-1.8	
Combined Cohort and C/C		1174			1.44	1.26-1.66		

* Private communication.

*From Blot and Fraumeni (1986).

cer in males. The relative risks were 0.6, 1.5 and near unity, respectively. The number of cases in each study is very small with no statistical significance. Therefore, it was decided to use a neutral relative risk of 1.0 for males for cancer other than lung until more data become available.

There are now six studies of passive smoking and heart disease in females. The individual and combined

relative risks are shown in Table 4. Studies new since 1985 are Lee *et al.* (1986), Martin *et al.* (1986a) and the important, large Helsing *et al.* (1988) paper from Maryland. The overall combined relative risk based on 1,622 cases is 1.23 with 95% confidence limits of 1.11 to 1.36 and a combined chi square of 16. Helsing *et al.* (1988) and Martin *et al.* (1986a) provide data for younger women and indicate high relative risks (average 2.45)

Table 2. Male relative risks for lung cancer from passive smoking.

	Locale	Total Cases	Highest Exposure		All Exposures			Mantel Trend
			RR	2-tail p	RR	95 % C.L.	1-tail p	
Cohort Studies								
Hirayama (1984a)	Japan	64	2.3	0.16	2.25	1.11- 4.9	0.023	
Gillis <i>et al.</i> (1984)	Scotland	6	—	—	3.3	0.7-16.5	—	
Combined Cohort		70			2.5	1.2 - 5.0		
Case Control Studies:								
Correa <i>et al.</i> (1983)	Louisiana	8	—	—	2.0	0.4-10	—	
Buffler <i>et al.</i> (1984)	Texas	8*	—	—	1.6	0.3 - 8.1	—	
Kabat and Wynder (1984)	United States	12	—	—	1.0	0.3 - 3.2	—	
Lee <i>et al.</i> (1986)	United Kingdom	15	—	—	1.3	0.4 - 4.6	—	
Akiba <i>et al.</i> (1986)	Japan	19	—	—	1.8	0.5 - 5.6	—	
Humble <i>et al.</i> (1987)*	New Mexico	8	—	—	4.2	1.0-16.8	—	
Brownson <i>et al.</i> (1987)*	Colorado	4	—	—	2.7	0.2-31	—	
Combined Case Control		74			1.8	1.0 - 3.3	—	
Combined Cohort and C/C		144			2.1	1.3 - 3.2		

*Private Communication.

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Table 3. Female relative risks for cancer other than lung from passive smoking.

	Locale	Total Cases	Highest Exposure		All Exposures			Mantel Trend
			RR	2-tail p	RR	95% C.L.	1-tail p	
Cohort Studies:								
Hirayama (1984a)*	Japan	2505	1.16	0.01	1.11	1.0-1.2	0.05	
Gillis <i>et al.</i> (1984)	Scotland	43	—	—	1.2	0.6-2.5	—	
Reynolds <i>et al.</i> (1987)	California	70*	—	—	1.7	1.1-2.7	—	
Combined Cohort		2618			1.13	1.03-1.24	—	
Case Control Studies:								
Miller (1984)*	Pennsylvania	84	—	—	1.25	0.7-2.3	—	
Sandler <i>et al.</i> (1985)	North Carolina	231	—	—	2.0	1.3-2.9	—	
Combined Case Control		315			1.7	1.2-2.45		
Combined Cohort and C/C		2933			1.16	1.06-1.27		

*Obtained by subtracting data for lung cancer from data for all sites.

*Provided by Dr. Reynolds.

*Age adjusted Mantel-Haenszel values for nonemployed wives.

for ages up to about 50. At higher ages there is no trend with an average relative risk of 1.17 holding out to age 84.

For male heart disease and passive smoking there are now four studies (see Table 4). The two new ones are Lee *et al.* (1986) and Helsing *et al.* (1988). The result of Svendsen *et al.* (1987) is shown for information, but is not used in calculating the combined relative risk because it pertains to a high risk group. The combined relative risk based on 443 cases is 1.31 with 95% confidence limits of 1.1 to 1.6 and a combined chi square of 9. The results are remarkably uniform. As in the

female data the relative risk is high at the younger ages, about 2.9, but declines to a nontrend average of 1.28 which extends from age 55 out to the older ages. Svendsen *et al.* (1987) show that there was very little difference between never smoking men married to nonsmokers and those married to smokers in the major coronary risk factors such as baseline blood pressure, total cholesterol, and LDL cholesterol. This work was reported in more detail in Martin *et al.* (1986b). Small differences were found in weight (195 vs. 190 if wives were smokers) and drinks per week (10 vs. 8 if wives were smokers). On the other hand, Garland *et al.* (1985)

Table 4. Relative risks for heart disease from passive smoking

	Locale	Total Cases	Highest Exposure		All Exposures			Mantel Trend
			RR	2-tail p	RR	95 % C.I.	1-tail p	
Females								
Cohort Studies:								
Hirayama (1984b)	Japan	494	1.3	0.038	1.16	0.9- 1.4	0.02	
Gillis <i>et al.</i> (1984)	Scotland	21	—	—	3.6	0.9-13.8	—	
Garland <i>et al.</i> (1985)	California	19	—	—	3.5	0.9-13.6	—	
Helsing <i>et al.</i> (1988)	Maryland	988	1.27	—	1.24	1.1- 1.4	0.005	
Combined Cohort		1522			1.23	1.1- 1.4		
Case Control Studies:								
Lee <i>et al.</i> (1986)	United Kingdom	77	—	—	0.9	0.7- 1.3	—	
Martin <i>et al.</i> (1986a)	Utah	23	—	—	2.6	1.2- 5.7	—	
Combined Case Control		100			1.29	0.8- 2.0		
Combined Cohort and C/C		1622			1.23	1.1- 1.4		
Males								
Cohort Studies:								
Gillis <i>et al.</i> (1984)	Scotland	32	—	—	1.30	0.7- 2.6	—	
Lee <i>et al.</i> (1986)	United Kingdom	41	—	—	1.24	0.5- 2.6	—	
Helsing <i>et al.</i> (1988)	Maryland	370	—	—	1.31	1.1- 1.6	—	
Combined Cohort		443			1.31	1.1- 1.6	—	
Svendsen <i>et al.</i> (1987) ^a	United States	13	—	—	2.2	0.7- 6.9	—	

*Based on Cochran chi-square of 9.2.

*MRFIT cohort of high risk individuals, included for information only.

found that never smoking women married to smokers had slightly lower weight, slightly lower blood pressure, and slightly higher cholesterol, all nonsignificantly different, versus never smoking women married to never smokers. All of these authors conclude that the increased passive smoking risks they observed cannot be ascribed to differences in the major coronary risk factors between passively exposed and nonexposed never smokers.

It is impressive that the relative risks for heart disease from passive smoking rise in an orderly manner from the lowest risk group, Japanese women at 1.16, through American women at 1.27, and American men at 1.31, to high risk American men at 2.2.

A correction for misclassification was attempted for all three disease categories. Following Wald *et al.* (1986), and presuming that the passive smoking studies were done somewhat more carefully than the general questionnaire studies they cite, it was assumed that 5% of ever smokers were misclassified as never smokers. Along with Wald *et al.* (1986) we assumed that the nonexposed nonsmokers were actually exposed to 1/3 the extent of the exposed nonsmokers except that for Greece, Japan, and Hong Kong, where less than 30% of women had ever smoked, the correction for nonexposed female nonsmokers was omitted. It is believed that older, nonsmoking women in Greece and Japan, and probably in Hong Kong also, because of their social habits, were exposed to relatively little tobacco smoke beyond that of their husband's. Since most of the misclassified smokers were found to be light smokers or longstanding exsmokers, reduced relative risks for the misclassified ever smokers were calculated, as noted in Appendix A. The modified passive smoking relative risks are shown in Table 5. The false relative risks due to smoker misclassification are somewhat lower than calculated earlier by Wells (1986) because of the assumption of light smokers and long term exsmokers

among those misclassified; following Wald *et al.* (1986), and the use of a more accurate formula. In general, the misclassification of smokers has a large negative effect on male relative risk which is more or less offset by the positive effect of exposure of the "nonexposed." For females the smoker misclassification effect is small to negligible, but because the relative risks are smaller and no correction was made to "eastern" data (Japan, Greece, and Hong Kong), the positive effects of exposure of "nonexposed" are also smaller.

Calculation of Deaths

The details for the calculation of female lung cancer deaths from the relative risks, both constant and declining, are shown in Table 6 as an example. Similar calculations were made for the other disease and sex categories and are shown in Appendix A. The results of all of the calculations are summarized in Table 7. These results are restated per million total population in Table 8. Where the relative risk appears to decline with age and where never smoker death rates at the younger ages are low, as in female heart disease and lung cancer, there is a reduction in mortality calculated by using the age specific relative risks. Otherwise, the higher exposed population at the younger ages outweighs the higher death rate at older ages and total mortality is increased. In terms of total deaths the effects of using age specific relative risks tend to cancel out. The total deaths, before adjustment for misclassification, for both males and females are about 19,500 for a total for both sexes of about 39,000.

The effects of misclassification on total deaths are substantial, raising the total to 53,000. Most of this increase is in heart disease where the numbers are large and the effects of smoker misclassification, although not necessarily small, are still heavily outweighed by the partial exposure of the "nonexposed."

To be conservative a best estimate for passive smok-

Table 5. Passive smoking relative risks modified for misclassification.

	Lung Cancer	Other Cancer	Heart Disease
Females			
1. Combined relative risk.	1.44	1.16	1.23
2. False relative risk due to projected 5% smoker misclassification.	1.01	1.002	1.01
3. Combined relative risk corrected for smoker misclassification, (1) + (2).	1.43	1.16	1.22
4. (3) corrected for exposure of "non-exposed" at 1/3 that of exposed.	1.48	1.21	1.32
Males			
1. Combined relative risk.	2.1	1.0*	1.31
2. False relative risk due to projected 5% smoker misclassification.	1.3	—	1.11
3. Combined relative risk corrected for smoker misclassification, (1) + (2).	1.6	—	1.17
4. (3) corrected for exposure of "non-exposed" at 1/3 that of exposed.	2.4	—	1.29

*Assumed value for lack of better data.

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Table 6. Annual U. S. female lung cancer deaths from passive smoking.

Age of Death	Never-smoker Death Rate per 100,000	Nonsmoker Population 1000's	Fraction Exposed	Exposed Population 1000's	Relative Risk Constant at 1:44		Relative Risk Declining	
					Excess Death Rate	Deaths	RR	Deaths
35-39	1.6	6150	0.94	5781	0.50	29	1.70	39
40-44	2.4	4622	0.92	4252	0.75	32	1.69	43
45-49	3.6	3846	0.89	3423	1.14	39	1.68	52
50-54	5.3	3856	0.87	3355	1.69	57	1.62	72
55-59	7.8	4161	0.84	3495	2.51	88	1.56	104
60-64	11.0	4192	0.77	3228	3.62	117	1.49	126
65-69	16.6	4160	0.70	2912	5.55	162	1.43	159
70-74	23.5	3441	0.59	2030	8.21	167	1.36	142
75-79	34	3004	0.49	1472	12.3	181	1.29	127
80-84	46	1886	0.29	547	18.0	98	1.18	43
85+	52	1003	0.10	100	21.9	22	1.08	4
Totals	13.0	40291	0.76	30595	3.0	992	—	911

ing deaths might be 46,000, half way between the 39,000 calculated directly from the relative risks and the 53,000 calculated using the modified relative risks. By disease the total would consist of 3,000 lung cancer, 11,000 other cancer, and 32,000 heart disease. For each million of total population the deaths by disease would be 13 for lung cancer, 46 for other cancers, and 134 for heart disease. These numbers may be useful for populations similar to that of the United States in terms of proportions of never smokers, exsmokers, and smokers, and in terms of the proportion of the population that is less than 35 relative to that over 35. For other populations the per million numbers are best not used, but the methodology can be used. That cancer other than lung and heart disease are legitimate contributors to deaths from passive smoking is supported in Hirayama, (1984a,b) in his large prospective study. He found significantly elevated risks for all three diseases, and his result for lung cancer is now believed to be valid, (USSG 1986; NRC, 1986). It is difficult to believe that his lung cancer result is valid while the other two are not.

Discussion

The cancer sites for passive smoking appear to differ somewhat from those for direct smoking. Using information on specific cancer sites from Dr. Hirayama (private communication) it appears that cancers common to both types of smoking are lung, liver, cervix, nasal sinus, and leukemia. Some of these cancers are only weakly associated with direct smoking. Cancers associated to some degree with direct smoking, but absent in passive smoking are buccal cavity, pharynx, larynx, esophagus, stomach (Hirayama, 1984a), urinary bladder (Kabat *et al.*, 1986), kidney and pancreas. Cancers related to passive smoking, but absent in direct smoking are brain (Hirayama, 1984a), endocrine glands (Sandler *et al.*, 1985), lymphoma and breast (Sandler *et al.*, 1985, 1986; Hirayama, private communication). The first three are significant at the 95% level. The combined breast relative risk of 1.4 is significant at only 88%. Higher relative risks for these four sites might be found for direct smoking if epidemiologists used nonpassively

Table 7. Summary: U.S. annual deaths from passive smoking

	Lung Cancer	Other Cancer	Heart Disease	Total
Females:				
1. Constant combined relative risk.	992	8599	9768	19359
2. Relative risk declining with age.	911	11165	7602	19678
3. (1) corrected for misclassification.	1232	12280	14995	28507
Males:				
1. Constant combined relative risk.	1606	0	17335	18941
2. Relative risk declining with age.	1606	0	18164	19770
3. (1) corrected for misclassification.	2499	0	22467	24966
Totals for both sexes:				
1. Constant combined relative risk.	2598	8599	27103	38300
2. Relative risk declining with age.	2517	11165	25766	39448
3. (1) corrected for misclassification.	3731	12280	37462	53473
Best current estimate, both sexes (rounded).	3000	11000	32000	46000

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Table 8. Summary: Deaths per million population in U.S. from passive smoking.
(based on 239,000,000 U.S. population in 1985)

	Lung Cancer	Other Cancer	Heart Disease	Total
Females:				
1. Constant combined relative risk.	4.15	35.98	40.87	81.00
2. Relative risk declining with age.	3.81	46.71	31.81	82.33
3. (1) corrected for misclassification.	5.15	51.38	62.74	119.27
Males:				
1. Constant combined relative risk.	6.72	0	72.53	79.25
2. Relative risk declining with age.	6.72	0	76.00	82.72
3. (1) corrected for misclassification.	10.46	0	94.00	104.46
Totals for both sexes:				
1. Constant combined relative risk.	10.87	35.98	113.40	160.25
2. Relative risk declining with age.	10.53	46.71	107.81	165.05
3. (1) corrected for misclassification.	15.61	51.38	156.74	223.73
Best current estimate, both sexes (rounded).	13	46	134	193

exposed never smokers as the referent category rather than all never smokers as is usually done. Another difference between passive smoking and direct smoking is that the ratio of lung cancer deaths to deaths from other cancer for females or from heart disease for both sexes is much lower in passive smoking than in direct smoking.

These differences in mortality effects are probably real and reflect differences in chemistry and physics between direct smoking and passive smoking. Environmental tobacco smoke is generated in the burning tip of the cigarette at a lower temperature than direct smoke and therefore contains higher proportions of complicated organic compounds that tend to be carcinogenic (Brunnemann *et al.*, 1978). More importantly, (see Appendix D) the mainstream smoke, although generated at a particle size of about 0.7 μm , is very concentrated and appears to agglomerate into larger particles. Deposition rates are high, about 80%. Deposition occurs primarily in the mouth or in the larger airways of the lung where the particles are cleared relatively quickly into the mouth. This material is then swallowed. Some of it may be eliminated and produce no health effects at all or it may cause the digestive type cancers observed. Only a portion of mainstream smoke appears to remain as small particles that can penetrate deeply into the alveolar region. Environmental tobacco smoke, on the other hand, is very dilute, with a mass median diameter of about 0.4 μm . Particles in this size range have very low deposition rates, on the order of 10%, but what does deposit does so deep in the alveolar region of the lung where clearance times are longer. Black and Pritchard (1984) estimate that cigarette tar has a 17 hour half-time rate of clearance from the alveolar region, much longer than clearance times from the ciliated parts of the lung, but much shorter than for inert particles. This means that smoke particles are very likely dissolving in the fluids in the alveolar region and are being cleared into the blood and lymph systems for circulation throughout the body.

In summary, there are two types of smoking: (a)

large particle smoking, or its equivalent, which is the major component of direct smoking, which results in massive deposition in the mouth and larger airways of the lung, rapid clearance, cancers of the mouth, central lung and digestive system, and possibly heart disease, and (b) small particle smoking, which is a minor component of direct smoking, but the entirety of passive smoking, and which results in low doses deep in the lung, slow clearance, some lung cancer, but primarily other cancers and adverse heart effects.

These differences in chemistry and physics also explain, at least in part, the rather high mortality observed for passive smoking relative to the deposited dose of particulate. Smoke retention by a passive smoker is only about 1/400 that retained by a direct smoker in a 16 hour day (0.64 mg for the passive smoker per USSG (1986, p. 196) and 240 mg for the direct smoker assuming twenty 15 mg-tar cigarettes and 80% retention). In comparison, the ratio of lung cancer death rates is about 1/35. For cancers other than lung in females the ratio is about 1/7, for heart disease in females about 1/14 and for heart disease in males about 1/3. Preliminary calculations which are shown in Appendix D indicate that the smoke retained deep in the alveolar region may have a dose ratio higher than 1/400, perhaps as high as 1/60. It may be that carcinogenic material that solubilizes and clears from the alveoli into the blood may cause not only some of the cancers other than lung that are observed in passive smoking, but also some of the heart disease from passive as well as direct smoking. The hypothesis of Benditt and Benditt (1973) that arterial plaques are caused by DNA-modifying agents is receiving increasing support. See, for example, the recent work of Penn *et al.* (1986) on cell transforming capability of human atherosclerotic plaque DNA and the earlier work of Albert *et al.* (1977) and Penn *et al.* (1981) on the formation of arterial plaques in cockerels with dimethylbenz(a)anthracene and benzo(a)pyrene.

Another possible factor that might help explain the disparate mortality effects versus dose is the level of disease susceptibility in passive smokers versus direct

smokers. The median age for passive smoking death from lung cancer for males is 66 and the deaths constitute 0.006% per year of the exposed population. The first 0.006% of male smokers have died of lung cancer by age 46 at which age the lung cancer death rate is doubling every four years. At age 66 the smoker lung cancer death rate is doubling about every 13 years. In other words, in passive smoking deaths we are dealing with only the very most susceptible people, whereas in direct smoking most of the victims are much nearer average susceptibility. Similar considerations apply to the other diseases here discussed.

A question often raised is that direct smokers are also passive smokers, so why do they not get the passive smoking related cancers. We have already pointed out that the use of nonexposed never smokers as the referent category for smoker relative risk would increase the apparent risk for smokers. Another possible explanation is the probability of competing risks. Most of the highly susceptible direct smokers would have died in their forties or fifties from smoking related disease and would not be available to die of passive smoking related disease in their sixties or seventies.

The passive smoking mortality calculated in this study, namely, 46,000, may be low. Repace and Lowrey (1985) calculate lung cancer deaths from passive smoking at 4,665, or about 50% higher than our estimate, primarily because of postulated intense exposure at the workplace, a factor not taken into account in this study since the relative risks are based largely on home exposure. If Repace and Lowrey are correct, the higher exposure would lead to corresponding increases in deaths from heart disease and other cancer. Also, only ischemic heart disease is considered here. As the all cause data in Appendix B indicate, other cardiovascular diseases and diabetes may be sensitive to environmental tobacco smoke and may increase the total deaths.

The new epidemiological studies on passive smoking support the earlier ones and indicate that not only lung cancer, but other cancer and heart disease are serious problems. In fact, lung cancer appears to be only the tip of the iceberg. To be on the safe side public health policy should be to protect nonsmokers from environmental tobacco smoke.

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Table A1. Annual U.S. male lung cancer deaths from passive smoking

Age of Death	Never-smoker Death Rate per 100,000	Nonsmoker Population 1000's	Fraction Exposed	Exposed Population 1000's	Relative Risk Constant at 2.1	
					Excess Death Rate	Deaths
35-39	1.8	5156	0.74	3815	1.09	42
40-44	2.9	4136	0.72	2980	1.78	53
45-49	4.5	3477	0.70	2440	2.80	68
50-54	7.0	3431	0.66	2260	4.46	101
55-59	11	3423	0.63	2155	7.15	154
60-64	16	3489	0.59	2054	10.7	219
65-69	23	3150	0.54	1695	15.9	269
70-74	33	2443	0.45	1099	24.3	267
75-79	49	1712	0.37	633	38.3	242
80-84	72	921	0.27	249	61.1	152
85+	95	516	0.08	41	96.0	39
Totals	15.9	31844	0.61	19420	8.26	1606

Appendix A

Details of death calculations

Tables A1 and A2 show the details of the death calculations for male lung cancer and female cancer other than lung and are similar in all respects to Table 6 in the text except that no declining relative risk calculation is shown for male lung cancer since the evidence that was available (Hirayama, 1984a) indicated no such decline.

In Table A3 the details are given for the development of the never smoker relative risks for heart disease that were used in the death calculations. As noted in the text, the 1963 never smoker heart death rates by 5-year intervals were obtained by dividing the never smoker coronary heart deaths in Hammond's (1966) appendix, Table 14, by the person years in his appendix tables 2a and 2b. Reduction factors to account for the change in heart death rates between 1963 (end of Hammond's study) and 1984 were then developed by 10 year age intervals from the age specific heart death rates in table 24 of Health U.S. 1986 (NCHS, 1986). These reduction factors were modified for the fractions thought to be due to smoking

which were taken from a staff report of the Office of Technology Assessment (OTA, 1985) to yield a combined never smoker reduction factor, interpolated back to 5-year age intervals, for application to the Hammond never smoker death rates. These modified rates, which are for enrollment age and therefore about 2 years younger than age of death, were then plotted against age of death on semi-log graph paper. Trend lines were then drawn through the female and the male points to yield the values in the last column of Table A3.

Tables A4 and A5 are simply the details of the heart death calculations as in Tables 6, A1, and A2 for cancer.

The deaths shown in Table 7 resulting from the corrections for misclassification were calculated from the relative risks in lines 4 of Table 5 taken as constant over the age range. The modification of the observed relative risks for smoker misclassification as shown in Table 5 are based on misclassified smoker relative risks calculated as follows. Based on as yet unpublished work of Wells on misclassification it was assumed that self-reported current smoker relative risks for male and female lung cancer in the U.S. and U.K. were 11 and 7, and 4.6 and 2.7 for male and female current smokers in Japan

Table A2. Annual U.S. female deaths from cancer other than lung from passive smoking.

Age of Death	Never-smoker Death Rate per 100,000	Exposed Population (Table 6) 1000's	Relative Risk Constant at 1.16		Relative Risk Declining	
			Excess Death Rate	Deaths	RR	Deaths
35-39	28	5781	3.9	225	4.5	1321
40-44	48	4252	6.7	285	2.9	1411
45-49	80	3423	11.2	363	2.0	1449
50-54	125	3355	17.6	589	1.56	1579
55-59	190	3495	26.8	937	1.30	1591
60-64	265	3228	37.7	1219	1.18	1352
65-69	355	2912	51.1	1487	1.12	1144
70-74	470	2030	68.7	1395	1.08	729
75-79	600	1472	89.0	1310	1.05	431
80-84	750	547	114.7	627	1.034	138
85+	900	100	141.7	142	1.022	20
Totals	256	30595	28.1	8599		11165

Table A3. Development of 1984 never-smoker heart death rates versus age.

Age Range	Death rates from Hammond (1966) at enrolled age per 100,000	Decline in heart DR's % 1963-84	Fraction of decline due to smoking	1984 Never-smoker Death Rate as % of 1963 (smoothed)	Hammond's N.S. D.R. corrected for decline	1984 Never-smoker heart death rate by age of death
<i>Females:</i>						
35-39	7.1			49	3.5	2.0
40-44	14.1	48	0	55	7.7	4.4
45-49	20.4			60	12.2	10.2
50-54	45.5	37	0	63	28.7	23
55-59	104			64	66	51
60-64	243	36	0	64	156	113
65-69	475			64	304	240
70-74	961	37	0	64	615	480
75-79	1648			65	1072	870
80-84	2774	35	0	70	1942	1550
85+	—	21	0	79	—	2770
<i>Males:</i>						
35-39	0			76	0	20
40-44	79.5	48	50	77	61	36
45-49	85.5			78	67	68
50-54	220	42	50	77	169	128
55-59	397			75	298	237
60-64	741	37.5	25	75	556	412
65-69	1089			76	827	730
70-74	1936	32	25	76	1472	1150
75-79	2639			77	2024	1850
80-84	4374	25	10	81	3543	2950
85+	—	14	10	86	—	4700

(Hirayama, 1984a). The 5% of ever smokers who were assumed misclassified as never smokers were assumed to consist of 23% light current smokers and 77% long term exsmokers. The excess risks for current self-reported smokers were reduced by 2/3 to yield relative risks for misclassified current smokers and by 11/12 for relative risks of misclassified exsmokers essentially as was done by Wald *et al.* (1986). This resulted in misclassified ever smoker relative risks of 2.4, and 1.85 for males and females in the U.S. and U.K. and 1.5 and

1.25 for Japan. Worldwide misclassified smoker relative risks were then calculated to be 1.8 for males and 1.6 for females based on the proportion of "western" and "eastern" cases. The false relative risks shown on lines 2 in Table 5 were then calculated using the formulae in Wells' unpublished work.

For female cancer other than lung, the smoker relative risk of 1.05 was taken from Hammond (1966) and used as is since the effect is too small to make any difference. For ischemic heart disease the ever smoker relative risks from Hammond

Table A4. Annual U. S. female heart deaths from passive smoking.

Age of Death	Never-smoker Death Rate per 100,000 (Table A3)	Exposed Population (Table 6) 1000's	Relative Risk Constant at 1:23		Relative Risk Declining	
			Excess D.R.	Deaths	RR	Deaths
35-39	2.0	5781	0.38	22	4.0	91
40-44	4.4	4252	0.84	36	2.0	97
45-49	10.0	3423	1.91	65	1.32	85
50-54	23	3355	4.4	148	1.17	114
55-59	51	3495	9.8	344	1.17	265
60-64	113	3228	22.1	713	1.17	548
65-69	240	2912	47.7	1385	1.17	1062
70-74	480	2030	97.2	1973	1.17	1505
75-79	870	1472	180	2647	1.17	2010
80-84	1550	547	334	1828	1.17	1374
85+	2700	100	607	607	1.17	451
Totals	291	30595	31.9	9768		7602

Table A5. Annual U. S. male heart deaths from passive smoking.

Age of Death	Neversmoker Death Rate per 100,000 (Table A3)	Exposed Population (Table A1) 1000's	Relative Risk Constant at 1.31		Relative Risk Declining	
			Excess D.R.	Deaths	RR	Deaths
35-39	20	3815	4.9	187	5.2	780
40-44	36	2980	8.9	265	3.0	879
45-49	68	2440	16.9	411	1.92	929
50-54	128	2660	32.1	724	1.42	951
55-59	237	2155	59.8	1289	1.28	1201
60-64	412	2054	105	2157	1.28	2009
65-69	730	1695	189	3195	1.28	2972
70-74	1150	1099	304	3341	1.28	3103
75-79	1850	633	500	3162	1.28	2933
80-84	2950	249	819	2039	1.28	1887
85+	4700	41	1377	565		520
Totals	521	19420	89.3	17335		18164

(1966) were taken as 2.3 for males and 2.0 for females. The excess risks were reduced by 2/3 to yield relative risks for misclassified ever smokers of approximately 1.4 for males and 1.3 for females. These were used worldwide with Wells' unpublished formulae to calculate the false heart disease relative risks shown on lines 2 of Table 5.

Appendix B

Relative risks for all causes of death and for emphysema and chronic obstructive lung disease

Data relating all causes of death with passive smoking for females have been reported for four prospective studies totalling 9537 cases as shown in Table B1. The combined relative risk is 1.165 with 95% confidence limits of 1.11 to 1.22. The only male data available are 75 cases from Gillis *et al.* (1984) with a relative risk of 1.0 so no male analysis was made.

The calculation of the total number of female deaths from all causes for passive smoking is shown in Table B2. The total, 34,164, is considerably larger than the total for cancer plus heart of 19,359 shown in Table 7. Some of the difference is due to uncertainties in the calculations, but other causes of

death that might contribute to the all cause total, based on data in a private communication from Dr. Hirayama, are cerebrovascular disease, other heart disease, diabetes, and ulcer.

Hirayama (private communication, also reported preliminarily at 5th World Conference on Smoking and Health, Winnipeg, 1983) provides data relating deaths from emphysema with passive smoking in women. His relative risk, based on 106 cases is 1.3 with 95% confidence limits of 0.85 to 2.05. Kalandidi *et al.* (1987) report incidence data for chronic obstructive lung disease based on 103 cases with an adjusted relative risk of about 1.4. Lee *et al.* (1986) report incidence data for chronic bronchitis from spouse exposure. Based on 17 cases the adjusted relative risk is 1.22. A weighted average of these three relative risks would be about 1.35. The only neversmoker death rate we have is from Hammond (1966) for emphysema at 2×10^{-5} . Assuming 76% exposure, the excess death rate for passive smoking using Eq. (2) would be 0.55×10^{-5} and the total deaths for an exposed population of 30.6 million would be about 170. Even if this number is doubled to take into account deaths from forms of chronic obstructive lung disease other than emphysema, it is still far below the total for cancer and ischemic heart disease.

Table B1. Female relative risks for all causes of death from passive smoking.

Cohort Studies:	Locale	Total Cases	All Exposures		Mantel Trend 1-tail p
			RR	95% C.L.	
Hirayama (1987)	Japan	9106	1.17*	1.12-1.23*	0.00001
Gillis <i>et al.</i> (1984)	Scotland	102	1.45	0.91-2.30	—
Garland <i>et al.</i> (1985)	California	79	1.06	0.65-1.73	—
Vandenbroucke <i>et al.</i> (1984)*	Holland	250	0.79	0.57-1.09	—
Combined Cohort:		9537	1.165	1.11-1.22	

*Dr. Hirayama (private communication) provided the data necessary to calculate these items.

*Data from 25 year follow up. Relative risk was 0.89 (0.50-1.62) for 15 year follow up. This study is weak in that exsmoking women were included among the "nonsmokers," and nonsmoking women exposed to exsmoker husbands were included in the "nonexposed." The weakness of the study is emphasized in that the smoking women had a lower overall death rate (33.4%) than the nonexposed nonsmokers (38.1%).

Table B2. Annual U.S. female deaths from all causes from passive smoking

Age Range	Neversmoker Death Rates from Hammond (1966) at enrolled age per 100,000	Decrement due to heart death rate 1963-84 per 100,000	Corrected Neversmoker death rate at enrolled age per 100,000	Neversmoker death rate corrected to age of death per 100,000	Population exposed 1000's	Fraction of population exposed	Relative Risk Constant at 1.165	
							Excess D.R.	Deaths
35-39	136	3.6	132.4	120	5781	0.94	17.1	991
40-44	178	6.4	171.6	155	4252	0.92	22.2	944
45-49	254	8.2	245.8	212	3423	0.89	30.5	1044
50-54	352	16.8	335.2	300	3355	0.87	43.3	1452
55-59	561	38	523	445	3495	0.84	64.5	2254
60-64	867	87	780	675	3228	0.77	98.8	3190
65-69	1492	171	1321	1070	2912	0.70	158.3	4609
70-74	2585	346	2239	1830	2030	0.59	275.2	5586
75-79	4790	576	4214	3250	1472	0.49	496.1	7303
80-84	8408	832	7576	6000	547	0.29	944.8	5168
85+	—	—	—	10,000	100	0.10	1623	1623
Totals					30595		111.7	34164
Deaths per million total population								143

Lee *et al.* (1986) report data on chronic bronchitis life long nonsmoking in males exposed to a smoking spouse. Based on nine cases the adjusted relative risk was 0.34. However, for general exposure (4 cases) a positive relative risk was observed. No analysis of these data was attempted.

Appendix C

Rate difference model for assessing female ischemic heart deaths from passive smoking

A rate difference or absolute risk model was investigated for female ischemic heart disease in order to compare it to the relative risk models in ability to translate experience from one type of culture to another. Female ischemic heart disease was chosen because considerable data exist and because heart disease is the largest contributor to total deaths. Also, the relative risk model seems already to be well established for lung cancer (Wald *et al.*, 1986; Blot and Fraumeni, 1986) so a comparison in another disease category appeared to be appropriate.

Data from the four cohort studies (see Table 4) were combined using the direct pooling equations described on page 183 in Rothman (1986). The two case/control studies were omitted. Although their combined rate difference was essentially the same as that for the cohort studies, no good way could be found to combine it with that from the cohort studies.

Death rates for exposed and not exposed populations were obtained by dividing the observed deaths in each category by person years which were equated to the mid-point populations multiplied by the years of followup. The rate difference was then obtained by subtracting the nonexposed death rate from the exposed death rate. Variances and weights were calculated by Rothman's formulae. The combined rate difference was obtained by summing the weighted rate differences and dividing by the sum of the weights. Confidence limits (95%) were equated to the rate difference ± 1.96 (variance)^{1/2}.

The results of these calculations are summarized in Table C1. The cohort data were also combined using Program 7 of Rothman and Boice (1982) with results essentially identical to those shown in Table C1 for direct pooling. The relative heterogeneity of the relative risks (*RR*) vs. the rate differences (*RD*) can be approximated by considering the range of *RR*-1 versus the range of *RD*. The range of *RR*-1 is from 0.16 to 2.6 for a factor of 16.3. The range of the rate differences is 3.7 to 262 or a factor of 71. The ratio for the two large studies, Helsing *et al.* (1988) and Hirayama (1984b), for *RR*-1 is 0.24/0.16 = 1.5 and for *RD* is 20.7/3.7 = 5.6. The 95% confidence limits for the rate ratio combination is tighter than for the rate difference combination. Also, the Hirayama study dominates the rate difference aggregation much more than in the rate ratio aggregation, providing 64% of the combined weight (last column of Table C1) in the rate difference case vs. only 17% of the combined weight in the rate ratio case.

Table C1. Rate difference calculations for female ischemic heart disease.

	Total Cases	Relative Risk from Table 4		Rate difference $\times 10^3$		Weights for RD $\times 10^{-4}$	RD \times weight $\times 10^{-1}$
		RR	95% C.L.	RD	95% C.L.		
Cohort Studies:							
Hirayama (1984b)	494	1.16	0.9-1.4	3.7	-2.1-9.6	1110	41.4
Gillis <i>et al.</i> (1984)	21	3.6	0.9-13.8	169.1	30.7-307.6	2	3.4
Garland <i>et al.</i> (1985)	19	3.5	0.9-13.6	262.2	36.0-488.4	0.8	2.0
Helsing <i>et al.</i> (1988)	988	1.24	1.1-1.4	20.7	-0.2-41.6	88	18.2
Combined Cohort	1522	1.23	1.1-1.4	5.4	-0.2-11.1	1201	65.0

Table D1: Regional particle deposition from mouth breathing of side stream smoke

Aero-dynamic diameter μm	Cube of diameter	Relative concentration ^a	Relative Volume (Weight) per 0.1 μm	Mass Distribution %	Fraction of inhaled particle mass deposited ^b			Mass deposited as % of total mass inhaled ^c
					mouth throat	tracheo-bronchial	alveolar	
0.20	.008	1.5	0.006	0.3	0	0	0.13	0.04
0.25	.016	6.5	0.051	2.4	0	0	0.122	0.29
0.30	.027	10.0	0.135	6.4	0	0	0.115	0.74
0.35	.043	13.0	0.280	13.2	0	0	0.108	1.43
0.40	.064	13.0	0.416	19.6	0	0	0.10	1.96
0.45	.091	6.5	0.296	14.0	0	0	0.105	1.47
0.50	.125	3.5	0.328	15.5	0	0	0.11	1.71
0.60	.216	1.25	0.270	12.7	0	0	0.115	1.46
0.70	.343	0.5	0.172	8.1	0	0	0.12	0.97
0.80	.512	0.25	0.128	6.0	0	0	0.13	0.78
0.90	.729	0.05	0.036	1.7	0	0	0.14	0.24
1.00	1.0	0	0	0	0	0	0.15	0.00
			2.118	99.9				11.08

^aFrom Hiller *et al.* (1982), Fig. 1.^bFrom Heyden (1984), Table 1, 250 cm³/second mean flow rate, 4 second breathing cycle.

This domination of the rate difference model by the Japanese study is evident from some rough death calculations. Use of the combined rate difference (5.4×10^{-4}) with the exposed female population from Table A4 (30.6 million) yields total deaths of 1.652 compared with 9.768 calculated from the constant rate ratio model. When the rate differences are plotted against age of death and weighted accordingly it is found that the "western" rate differences increase sharply with age whereas the Japanese rate difference stays constant at about 4×10^{-4} . Constructing a weighted average of these "western" and "eastern" death rates for each of the 5 year age ranges and multiplying by the corresponding exposed populations yields a total of about 2.100 deaths compared with

7.602 in the second relative risk model. Use of the Japanese data alone yields about 1.200 deaths. Use of only the "western" data (Gillis *et al.*, 1984; Garland *et al.*, 1988; Helsing *et al.*) at a constant rate difference yields 7.950 deaths while use of "western" data with the rate difference varying with age yields about 30,000 deaths. Thus, the death calculations using rate differences are quite volatile. Also, it is evident that with the rate differences it is not feasible to carry over the "eastern" experience, in ischemic heart disease at least, for use in a "western" setting. Accordingly, it was concluded that the absolute risk model is not as suited to combining risks for passive smoking as the relative risk models.

Table D2: Regional particle deposition from nose breathing of sidestream smoke.

Aero-dynamic diameter μm	Mass distribution % ^a	Fraction of inhaled particle mass deposited ^b				Mass deposited as % of total mass inhaled	
		nose	mouth throat	tracheo-bronchial	alveolar	nose	alveolar
0.20	0.3	0	0	0	0.19	0.00	0.06
0.25	2.4	0.005	0	0	0.172	0.01	0.41
0.30	6.4	0.01	0	0	0.155	0.06	0.99
0.35	13.2	0.015	0	0	0.138	0.20	1.82
0.40	19.6	0.02	0	0	0.12	0.39	2.35
0.45	14.0	0.03	0	0	0.122	0.42	1.70
0.50	15.5	0.04	0	0	0.125	0.62	1.94
0.60	12.7	0.05	0	0	0.128	0.64	1.63
0.70	8.1	0.06	0	0	0.13	0.49	1.05
0.80	6.0	0.077	0	0	0.133	0.46	0.80
0.90	1.7	0.093	0	0	0.137	0.16	0.23
1.00	0.0	0.11	0	0	0.14	0.00	0.00
						3.45	12.99

^aFrom Table D1.^bFrom Heyden (1984), Table 2, 250 cm³/second mean flow rate, 4 second breathing cycle.

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Table D3. Smoke Particle deposition patterns in direct and passive smoking.

	Direct Smoking	Passive Smoking	Direct Passive
Entry site	Mouth	Nose	
Particulate inhaled per day, mg.	240	2.8	86
Particle Size inhaled, μm	0.7	0.4	
Particle size exhaled, μm	0.7	0.4	
Retained in nose, %	0	3.5	
Retained in mouth, %	25	0	
Retained in tracheo-bronchial region, %	35	0	
Retained in near alveolar region, %	11	0	
Retained in deep alveolar region, %	9	13	
Total retained, %	80	16.5	
Particulate retained, total, mg.	192	0.46	417
Particulate retained, alveolar, mg.	48	0.36	133
Particulate retained, deep alveolar, mg.	22	0.36	61

Appendix D

Dose considerations

As noted in the text, there is a wide difference between the observed disease ratio between passive and active smokers and the ratio of cigarette smoke particulate retained by each. Also, the cancer sites appear to differ. On the assumption that part of these differences may be due to differences in deposition sites between passive smoking and active smoking, calculations were carried out to try to pinpoint these differences.

The calculations for passive smoking are reasonably straightforward. Stöber (1984) has summarized all the uncertainties in this type of calculation. Nevertheless, the best approach appears to be to use the data of Hiller *et al.* (1982) for the particle size range of side stream smoke, centering around $0.4 \mu\text{m}$, and the mathematical lung model of Heyder (1984) for inert particles. Integration of these two data sets yields a distribution of deposited weights by particle size for mouth breathing (see Table D1) which, when summed, yields exactly the total deposition observed by Hiller *et al.* (1982) indicating that the Heyder model holds for passive smoking. The same inhaled particle size distribution can then be applied to Heyder's nose breathing case (see Table D2) which yields nasal deposition of 3.5% and deposition in the alveolar region of the lung of 13.0%. The model predicts zero deposition for both the mouth/throat and the tracheo-bronchial regions. From the deposition curves of Gerrity *et al.* (1979) (Fig. 2) for iron oxide extrapolated to a particle size of $0.25 \mu\text{m}$ (which is equivalent to an aerodynamic diameter of $0.4 \mu\text{m}$) it appears that all of the lung deposition from passive smoking probably occurs deep in the alveolar region at generation 19 or beyond. Black and Pritchard (1984) have determined the half-time for alveolar retention for direct cigarette smoke to be 17 hours indicating that the smoke particles dissolve and clear into the blood or lymph system. There is every reason to believe that the passive smoke particles clear the same way.

With direct smoking there has so far been no model developed that explains the observed phenomena, namely that the inhaled particle size is about $0.7 \mu\text{m}$, that 70% to 80% of the inhaled smoke is retained, that 15 to 35% is retained in the mouth, and that the exhaled particle size is also about $0.7 \mu\text{m}$. The Heyder model at $0.7 \mu\text{m}$ would predict total retention of only 12%. To achieve 75% retention, the Heyder

model would require an effective particle size of $6.5 \mu\text{m}$. Main stream smoke is known to agglomerate, but if it agglomerated to $6.5 \mu\text{m}$, the exhaled smoke, according to the Heyder model would be about $6 \mu\text{m}$, much too large compared to that observed. Mitchell (1962) observed that direct smoke particles grow in the mouth to about $1.15 \mu\text{m}$ and that the smoke exhaled from the lung after a 5 second retention period had a mass median diameter size of $0.65 \mu\text{m}$. Let us assume that the $0.65 \mu\text{m}$ part of the smoke follows Heyder's model and that 20% of the total smoke inhaled was exhaled, all from the $0.65 \mu\text{m}$ fraction. The inhaled part of the smoke corresponding with the $0.65 \mu\text{m}$ part exhaled would have the same particle size and would deposit about 12%, deep in the alveolar region. This is 12% of 22.7% of the total smoke inhaled, or 2.7% of the total inhaled smoke. The balance of the inhaled smoke (77%) would have a larger average particle size, about $1.3 \mu\text{m}$. Black and Pritchard (1984) found, based on clearance data, that the rates of alveolar deposition to alveolar plus tracheo-bronchial deposition in direct smoking is 0.36. Also, as noted, some amount, say 25% of the total inlet smoke should deposit in the mouth and throat, all of which would have to come from this larger size fraction. Summarizing these numbers, of the $100 - 20 - 25 = 55\%$ of total smoke particulate that reaches the lung and is not exhaled, $0.64 \times 55 = 35\%$ deposits in the tracheo-bronchial region and $0.36 \times 55 = 20\%$ deposits in the alveolar region. We have already accounted for 3% of the alveolar deposition from the $0.65 \mu\text{m}$ particles. The remaining 17% would come from the larger particles. Based on the alveolar/tracheo-bronchial split and using the curves of Gerrity *et al.* (1979) it would be expected that about 2/3 of the alveolar deposit or 11% would deposit in the "near" alveolar region, generations 16-18, and 6% in the "deep" alveolar region, generations 19-21, for a total "deep" alveolar deposition of 9%. These calculations are summarized in Table D3.

Just what the mechanisms are for so much direct smoke deposition remains unclear. Certainly impaction and sedimentation (the Heyder model) do not account for it. Stöber (1984) suggests that electrical charges in the newly generated smoke particles (see Melandri *et al.*, 1983) may account for some of it. Another possible mechanism is the cloud settling phenomenon as described by Fuchs (1964).

Whatever the mechanism, a reasonably clear idea of the regional deposition patterns from direct and passive smoking

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can be obtained as shown in Table D3. The nasal deposition from passive smoking could account for the observed nasal sinus cancer. Also, if the observation of Balin *et al.* (1986) is correct that there is a direct passage for toxics from the nose to the brain, it could also account for the observed brain cancer. In the deep alveolar region the ratio of direct to pas-

sive deposition is much closer to the inhaled ratio than to the "total retained" ratio. It is from the deep alveolar region that the smoke particles are solubilized and cleared into the blood and lymph systems possibly to cause cancers of the liver, breast and endocrine glands, leukemia, lymphoma and arterial plaques.

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EDITORIAL

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Cardiovascular Risks of Environmental Tobacco Smoke

The adverse effects of Environmental Tobacco Smoke (ETS) or passive smoking are being increasingly recognized by the scientific community. The detection of a considerable number of carcinogens at significant concentrations in tobacco smoke led to studies on risk assessment of ETS. There are numerous studies on the carcinogenic impact of ETS, among them several published in *Environment International*. The reason for starting with carcinogenic risk was the availability of the needed methodology for carcinogenic risk assessment. These methods, initially developed for ionizing radiation, were applied to chemical carcinogens and physical agents, and later on to mixtures. Despite their shortcomings, methods for cancer assessment have found acceptance by international organizations and by national regulatory agencies and are routinely applied in the regulatory process.

In contrast to cancer assessment, the assessment of risk associated with the exposure to agents causing cardiovascular diseases is in its infancy. There are no convincing dose-response models for these diseases and available animal models do not readily lend themselves to a quantification of cardiovascular risks. Available data indicates that two to three times as many people die from heart diseases as compared to those who die from cancer. If one takes into account the age of the affected individuals, this ratio is increased to about five to seven. In other words, the population in the industrialized nations loses five to seven times the number

of years of life to heart disease as compared to cancer.

This issue of the Journal contains a paper on the potential risks associated with exposure to ETS. The paper by Wells is an attempt to quantify this risk based on available statistical data. Because this paper is probably the first of its kind, the editors were particularly concerned over the validity of the original data, their application to risk assessment, and the statistical treatment of the subject.

The editors received recommendations from three reviewers. Two reviewers recommended publication subject to revisions recommended by them. A third reviewer recommended rejection of the paper on the basis that the paper was too speculative. This latter reviewer did not provide any specific recommendation on how to improve the quality of the paper. Despite the "mixed" review, we chose to publish the paper.

Given the current status of cardiovascular risk assessment, there is no doubt that the estimates provided by Wells will be less than accurate. However, there is no reason to doubt that ETS may be associated with a considerable cardiovascular risk.

The role of the scientific community is to provide the societal decision makers with the best available scientific information. The availability of the paper on the health risks of ETS will provide these decision makers and the general public with the needed information. It is not unreasonable to expect that this new information will become the basis for additional restrictions of smoking in public places.

A. Alan Moghissi

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Katzenstein, A.W.

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LETTERS TO THE EDITOR

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AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING; A RESPONSE

Dear Editor:

The health implications of environmental tobacco smoke (ETS) remain controversial. Neither the published reports nor statements from public health officials and agencies have resolved the question of ETS health effects, nor are they likely to in the near future.

A. Judson Wells' paper, "Estimate of Adult Mortality in the United States from Passive Smoking" (1988) is yet another effort to draw scientific verity from a reassessment of published epidemiological data. But this new look does not change the quality or meaning of the existing evidence, which remains equivocal. Neither does it substantively support the author's statement that exposure to ETS "can have adverse long term health effects that are more serious than previously thought".

The conclusions of nonsmokers' increased risk of lung cancer from ETS exposure found in the reports of the National Academy of Sciences (NRC 1986) and of the Surgeon General (USSG 1986) were based on epidemiological studies that produced a wide range of findings. The relative risk (RR) values summarized in Table 12.4 of the NAS report ranged from 0.50 to 3.25, with 17 out of 20 risk estimates (for subgroups by sex) lacking statistical significance. In seven additional reports since the NAS document was published, relative risk values ranged from "<1.00" to 1.65, with only the latter being statistically significant. The RR values from all 29 subgroups in the 20 studies included in the NAS report plus those published later are summarized in Table 1 herein.

All of the epidemiological studies that comprise the data base for estimating nonsmokers' risk of lung cancer in relation to ETS are actually estimates of association based on spousal smoking. In not a single study was either exposure to ETS or retained dosage determined. A few studies have attempted to estimate

the degree of exposure to spousal smoking in terms of hours per day or total years of exposure, but none of the studies measured ETS exposure in objective and quantitative terms or even estimated ETS exposure with any degree of reliability. Proximity to a smoker sitting across the dining table does not permit an estimate of the nonsmoker's exposure to ETS, which will vary according to room volume, ventilation rates, the physical and chemical changes in ETS as it ages, and other factors that influence the concentrations and duration of ETS exposure. A spouse's smoking in another room or in another building can have even less or no significance at all in assessing the possible role of passive smoking on a subject's health.

It should be recognized, also, that association can never establish causality. At best, association can only suggest the possibility of causality. Feinstein (1988), discussing public alarms based on epidemiological studies, recently pointed out that "a causal suspicion is supported if an impressive statistical association appears in the 2 by 2 tabulation for subgroups of people reported as being exposed or non-exposed, diseased or nondiseased".

There are many ways to look at data and try to draw meaning from the aggregation of values. After deciding that the 13 studies which survived critical assessment did not, individually or collectively, support a definitive conclusion on the risk of lung cancer in relation to spousal smoking, the NAS Committee performed a meta analysis on the aggregated data, leading to an estimated risk increase of about 34% for nonsmokers married to smokers. This estimate has been questioned on a variety of grounds by a number of investigators (Letzel et al. 1988).

It can be argued that even if a first order relationship does not exist between disease and passive smoking in the epidemiological studies, the data used by Wells are the best evidence available. And it can be argued that even the array of values shown in Table 1 is not impressive in the sense that Feinstein specifies, there are other ways of testing the data, as has been done by Wells.

Table 1. Statistical significance of risk values for lung cancer in relation to spousal smoking.

Investigator	Not Statistically Significant		Statistically Significant	
	Male	Female	Male	Female
*Chan and Fung (1982)		0.75		
*Buffler et al. (1984)	0.50	0.78		
Dalager et al. (1986)	<1.00			
*Kabat and Wynder (1984)	1.00	0.79		
Gao et al. (1987)		0.9 ^a		
*Gillis et al. (1984)		1.00		
*Lee et al. (1986)		1.00		
Gao et al. (1987)		1.1 ^a		
Shimizu et al. (1988)		1.1		
*Garfinkel (1981)		1.17 ^c		
*Pershagen et al. (1987)		1.20		
Vu et al. (1985)		1.20		
*Lee et al. (1986)	1.30			
*Garfinkel et al. (1985)		1.31 ^c		
*Akiba et al. (1986)	1.80	1.50		
*Koo et al. (1984)		1.64		
Brownson et al. (1987)		1.68		
Humble et al. (1987)	>1.20	1.80		
*Correa et al. (1983)	2.00	2.07 ^c		
*Hirayama (1981)			2.25	1.63
Lee et al. (1987)				1.65
*Trichopoulos et al. (1981)				2.11
*Gillis et al. (1984)		3.25		

* Risk values from Table 12.4, National Academy of Sciences Report (1986)

^a Exposure in adult life.

^b Exposure in childhood.

^c Statistically significant trends in one or more data subsets within the study.

There remains, however, the fundamental question of the quality of the individual underlying studies whose data are under consideration. Many of the epidemiological studies assessing the risk of lung cancer from spousal smoking have been criticized for a variety of methodological flaws and weaknesses, especially with regard to the potential for misclassification (Überla 1987; Balter et al. 1986; Lebowitz 1986; OTA 1986).

Misclassification of subjects is a source of error where patients claiming to be never smokers are in fact current or exsmokers. Wells conceded the likelihood of 5% misclassification. But misclassification of smoker status has been found at levels from 10% to 40% (Schwartz et al. 1988; Weiss 1988). NAS noted the likelihood of misclassification and lowered its estimate of the elevated risk to 25% from 34%, but it failed to indicate whether the lower value was

statistically significant. (NAS found the combined risk from American studies a 14% increase, which was not statistically significant.)

Misclassification of disease can also be a source of error. There was a marked potential for misclassified disease in the studies having statistically significant risk ratios in the NAS and Surgeon General's reports. In Hirayama's study of Japanese women, his 1984 report suggests that only 21 of the 200 lung cancer cases (10.5%) were histologically confirmed, while the Surgeon General's report states that "none" were verified. Akiba et al. (1986) studying survivors of the Hiroshima and Nagasaki atom bombings, noted 43% of the lung cancer cases had not been histologically confirmed. Weiss (1988) notes that "thirteen percent of the cases [in Garfinkel's study] proved on review not to involve lung cancer".

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Misclassification of exposure can be a source of uncertainty in studies that attempt to find exposure-response relationships. There is little basis for considering estimates of spouses' smoking to be reliable. Pron et al. (1988) concluded that "test-retest estimates of reliability [over a six-month time span] would suggest that misclassification of such exposures may be extensive". Vogt (1977) found "twenty-two percent of persons gave different answers on the two questionnaires [on the number of cigarettes smoked per day] given about an hour apart".

Among the variety of flaws and weaknesses found in the various epidemiological studies on ETS and lung cancer, it is worth noting the age bias found by Ahlborn and Überla (1988) in Hirayama's study and their conclusion that "the risk increase ... disappears completely when one removes selection bias by age". Überla (1987), highlighting the weaknesses of the epidemiological studies comprising the NAS data base, had earlier concluded, "False plus false does not equal true."

In addition, most of the epidemiological studies have failed to take into account significant confounding factors in assessing lung cancer risk in relation to ETS. Many risk factors for lung cancer have been identified, including exposure to heavy metals, organic chemicals, combustion by-products, natural and man-made radiation, diet, and nutritional status, personal health history, emotional, and psychological factors. Holst et al. (1988) recently reported significantly increased risk in relation to keeping pet birds and to reduced vitamin C intake. Gao et al. (1987) found no significant increased risk for Chinese women in relation to passive smoking or type of employment but did find significantly increased risk in relation to previous lung disease, cooking practices, and shorter menstrual cycles, reflecting hormonal factors. Some of these factors may act independently, but many may interact. Any attempt to assess the role of one factor must take into account all other relevant factors.

None of the epidemiological studies on spousal smoking took into account confounding factors other than attempting to match cases with controls by age, residence, and general socio-economic status. Of the 20 epidemiological studies, those by Hirayama and by Lam et al. (1987) have the two largest number of lung cancer cases, with the increased risk in both being statistically significant. Both studies are of Oriental populations, which suggests that many factors like cooking practices and fuels for cooking and heating should have been controlled.

All of the studies included in Wells' Table 4, on which he based his estimate of heart disease deaths

related to passive smoking, similarly fail to consider the confounding effect of the many cardiovascular disease risk factors that have already been established for that disease.

Some observers have commented that increased risk of lung cancer from ETS exposure seems implausible because the ETS components are so dilute in ambient air compared to the concentrations of these substances in mainstream smoke. In addition, it has been found that nonsmokers retain far less of inhaled ETS than active smokers retain of mainstream smoke. Wells noted that "smoke retention by a passive smoker is only about 1/400 that retained by a direct smoker in a 16 hour day". This is more than one order of magnitude greater than Rickert's calculation (1988) that nonsmokers exposed to ETS retain about 1/8000 the amount of particulate matter retained by the active smoker. Lee (1988) cited estimates of the same range: 1/5000 for males, 1/10 000 for females. All of these estimates are probably on the high side, since none of the studies appears to have considered the chemical and physical changes that occur as ETS ages and the losses of ETS through evaporation, fallout, and deposition over time.

Other observers have commented on the implausibility that lung cancer in nonsmokers might be caused by ETS. Aviado (1988) noted that none of 17 constituents of ETS "designated as suspect carcinogens ... [has] been adequately shown to cause pulmonary cancer via inhalation in animals". Crawford (1988) noted that "no atypical cellular changes have been found in the lungs of nonsmokers". Lee (1987) concluded "that exposure to smoke constituents of nonsmokers is too low to explain the moderate increase in risk of lung cancer seen in epidemiological studies in self-reported never smokers married to smokers. This increase in risk is much more plausibly explained by misclassification of smokers as nonsmokers than by a direct effect of passive smoking".

Wells has attempted to make his calculation of annual deaths from exposure to ETS appear more reasonable by comparing it to the larger estimate of Repace and Lowrey, but their estimate has been severely criticized because the controls were Seventh Day Adventists (SDA) whose life style is so radically different from that of the non-SDAs married to smokers that the comparison is considered inappropriate (OTA 1985; Balter et al. 1986; Überla 1987).

Taking these and other factors into account, Gostomzyk (1986) concluded, following the International Experimental Toxicology Symposium on Passive Smoking in Essen, FRG, that "even toxicology has not been able to ascertain with any greater degree

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of probability than did epidemiology that there exists a link between damage to health and passive smoking".

Perhaps it is the weight of these facts, interpretations, and opinions that caused no less an authority than the American Cancer Society to assert last year that "the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers..." (ACS 1988).

A final comment: both the title and the content of the editorial that accompanied the Wells paper suggests that the paper provides stronger evidence of risk of cardiovascular disease (CVD) for nonsmokers married to smokers than the paper in fact offers. In 1986, both the NAS and USSG reports noted the lack of convincing evidence of significant CVD risk from ETS exposure. More recently, Fielding and Phenow (1988) commented on papers reporting an association between ETS exposure and CVD risk, concluding that "no firm conclusion that a causal relation exists is yet warranted".

Wells' calculations with respect to CVD are based on data from epidemiological studies that have the same weaknesses as the lung cancer studies. There is, thus, no basis for greater confidence in his estimate of heart disease deaths in relation to ETS than his estimate of lung cancer deaths.

It is commendable that those who are not satisfied continue to seek more meaning from the data. But in an issue as serious as this, it is important to note when the data fail to meet the standards for scientific inference.

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AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING: A RESPONSE

Dear Editor:

Wells (1988) estimates that exposure to environmental tobacco smoke (ETS) causes 46 000 deaths per year in the U.S.; 3000 from lung cancer, 11 000 from other cancers, and 32 000 from heart disease. These estimates are scientifically unjustified. Far too much faith is placed on results from often fragile epidemiological studies, with major sources of bias ignored or totally underestimated. In contrast, far too little faith is placed on evidence that nonsmokers have very much lower exposure to tobacco smoke

constituents than do smokers, and that smokers are much more exposed to ETS than nonsmokers.

The evidence that exposure to ETS increases the risk of developing heart disease is extremely unconvincing. Of the studies cited by Wells, some are based on unacceptably small numbers of cases, e.g., Garland et al. (1985) where only two deaths occurred in women married to never-smoking husbands, while the only two studies with substantial numbers of deaths are both open to question.

When referencing the Japanese prospective study, Wells uses Hirayama's 1984 report of a statistically significant positive trend in wife's age-adjusted risk according to husband's smoking, but does not comment on the fact that, in 1981, Hirayama reported no association whatsoever. As shown in Table 1, the

Table 1. Female relative risks for heart disease from passive smoking in Japanese study.

Follow-up period	Total cases	Husband's smoking habit		
		Non-smoker	Ex or 9/day	20+/day
1966-79	406	1	0.97	1.03
1980-82 ¹	88	1	2.85	5.07
1966-82	494	1	1.10	1.30

¹ Estimated from 1966-79 data (Hirayama 1981) and from 1966-82 data (Hirayama 1984). The 1984 paper provided relative numbers of deaths as 118, 240, and 136.

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Follow-up period	Total cases	Husband's smoking habit		
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¹ Estimated from 1966-79 data (Hirayama 1981) and from 1966-82 data (Hirayama 1984). The 1984 paper provided relative numbers of deaths as 118, 240, and 136.

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1966-79 and 1980-82 data are totally inconsistent and statistical tests confirm the highly significant ($p < 0.001$) interaction between relative risk and period of follow-up. A possible explanation might be that the 1981 data, but not the 1984 data, were standardised additionally for occupation, but if this was important, why did Hirayama not standardise for occupation in 1984?

The Maryland prospective study (Helsing et al. 1988), which reported a 24% increase in heart disease risk in women, based on 988 deaths, and a 31% increase in men, based on 370 deaths, in relation to living with a smoker, has a number of features that should be considered when interpreting the data. No attempt was made to follow-up people moving outside Washington County, thus presumably missing large numbers of deaths. No dose-response relationship was reported. Adjustment for age, marital status, years of school and quality of housing had an enormous effect on relative risk, changing estimates from 1.17 to 1.31 in men and from 0.66 to 1.24 in women. No direct adjustment was made for household size, despite the fact that the larger the household, the more likely it is to contain a smoker. Furthermore, no direct adjustment was made for the possible correlation of household size with various coronary risk factors. Also, data were unavailable on a whole range of factors, such as diet and exercise, which might differ in families with and without smokers. In short, several potential confounders were apparently not controlled for.

Wells does not consider the problem of publication bias. This may be particularly acute for heart disease. After all, it is a vastly more common disease than lung cancer in nonsmokers, but the numbers of deaths in Wells' tables are only slightly greater. The possibility can surely not be excluded that other researchers, perhaps with much larger and better data bases, have looked at the relationship and found nothing.

The data for cancer other than the lung are even less convincing than for heart disease. In view of the much greater passive smoke exposure of smokers than nonsmokers, observations that nonsmokers exposed to passive smoking have increases in cancers at sites not increased in smokers seem to me to suggest that something is wrong with the epidemiological studies. And, indeed, the paper showing the strongest association (Sandler et al. 1985) is open to a number of serious criticisms (Lee 1985). Wells, however, remains content to include all epidemiological studies in his meta-analyses, regardless of quality, and attempts to explain obviously spurious relationships by an unsupported, and implausible hy-

pothesis, involving an especially susceptible group of individuals who all die early if they smoke but die later by passive smoking if they do not. Mortality patterns for lung cancer in terms of age, dose, and duration of smoking are in fact well described by models involving no component for variation in susceptibility at all.

Wells' estimate of 3000 lung cancer deaths per year based on the epidemiological data contrasts with that of 12 by Arundel et al. (1987) based on extrapolation using relative amounts of particulate matter retained in the lung by nonsmokers and smokers. As I argue at length elsewhere (Lee 1987; 1988a; 1988b; 1989a; 1989b), it is far more plausible to conclude that the association observed between lung cancer and exposure to ETS arises predominantly because of bias than it arises because of a carcinogenic effect of such low doses of ETS.

Misclassification of smokers as nonsmokers is likely to be a major source of bias in most studies and is one for which Wells' correction is totally inadequate. He does not allow at all for the possibility of misclassified current typical regular smokers, whereas a recent summary of data from large studies shows an average rate of about 4% (Lee 1989a). Nor do his calculations take into account recent data (USSG 1989) showing much higher relative risks in active smokers than in older studies. Preliminary calculations based on these data suggest that the total number of lung cancers occurring in self-reported never smokers in the U.S. may have been substantially overestimated. Rather than 12 000 the figure may be nearer 8000. If reasonable corrections are made for misclassification, the figure of lung cancer deaths among actual never smokers may be less than 6000.

Wells considers his overall estimate of 46 000 deaths conservative. I disagree. When better data are available, it may prove to be about 46 000 too high.

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ISCHEMIC HEART DISEASE; RESPONSE TO LEE

Dear Editor:

Dr. P. Lee questioned the reasons for a discrepancy of my reports in 1981 and in 1984 on husbands' smoking and ischemic heart disease risk in nonsmoking wives.

The 1981 report was based on a 14 year follow-up (n=400) and the 1984 report was based on a 16 year follow-up (n=494) of nonsmoking wives. The relative risks of ischemic heart disease when husbands were nonsmokers, exsmokers, or daily smokers of 1-19 cigarettes and 20 or more cigarettes were 1.00, 1.06, and 1.18 (trend p: 0.061 not significant) in the 14 year follow-up; and 1.00, 1.10, and 1.31 (trend p: 0.019 significant) in the 1984 report.

Table 1. Ischemic heart disease mortality in women by age group, by occupation, and by husbands' smoking habit (patient herself a nonsmoker).

Husband's occupation	Husband's age group	Husband's smoking habit					Total		
		Nonsmoker	Exsmoker 1-19/day	20+/day					
Agricultural worker	40-49	8	2,502	25	5,941	17	3,636	50	12,079
	50-59	15	3,497	27	6,812	27	3,514	69	13,823
	60-69	36	4,084	79	6,845	27	2,152	142	13,081
	70+	5	323	11	446	2	89	18	858
	Total	64	10,406	142	20,044	73	9,391	279	39,841
Other	40-49	5	3,727	15	9,093	15	2,128	35	19,948
	50-59	11	4,294	29	8,830	23	6,306	63	19,430
	60-69	29	3,036	46	5,598	20	2,499	95	11,133
	70+	9	432	8	619	5	137	22	1,188
	Total	54	11,489	98	24,140	63	16,070	215	51,699
The weighted point estimate of rate ratio and test-based 90% confidence limits		1.00	1.11	1.33	1.36	1.68	Mantel extension: chi 2,539 One tail p value 0.00916		
				0.92		1.09			
Mantel-Haenszel chi		-	0.882	2.331					
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Possible reasons would be (1) a longer follow-up period and more cases in the 1984 report than in the 1981 report, or (2) husbands' age and occupation were standardized for data in 1981, while data reported in 1984 was standardized by age only. However, the latter is definitely not the reason responsible for the discrepancy, as age-occupation standardized data in 1984 showed almost similar results, corresponding relative risks (r.r.s) being 1.00, 1.11, and 1.36 (trend p : 0.009), respectively (Table 1). The results were also similar when standardized by wives' age, corresponding r.r.s being 1.00, 1.09, and 1.34 (trend p : 0.019). Therefore, it should be concluded that the more cigarettes the husbands smoke, the higher the ischemic heart disease risk in non-smoking wives.

In 1980-1981, r.r.s of ischemic heart disease in nonsmoking wives were 1.00, 1.29, and 1.87 (trend p : 0.041) when husbands were nonsmokers, exsmokers/10-19 daily, and 20+ daily respectively. One may further consider as the possible reasons for

this discrepancy the influence of the changing quality of side-stream smoke coming out of the ignited end of cigarettes in recent years due to the intensive chemical manipulation of the products (e.g., inclusion of tobacco additives) in order to lower tar and nicotine, to improve the flavor, etc. Also, the recent increase in fat consumption in Japan may interact on the risk of ischemic heart disease when exposed to passive smoking.

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REBUTTAL TO LEE/KATZENSTEIN COMMENTARY ON PASSIVE SMOKING RISK

Dear Editor:

Lee (1989) and Katzenstein (1989), in their commentary on Wells' (1988) paper, take issue not only with Wells' estimates of the magnitude of the mortality effect of passive smoking on nonsmokers, but question whether mortality occurs at all. Their arguments are based upon the alleged fragility of the epidemiological studies of passive smoking and disease; the potential for misclassification of subjects; disease, or exposure; possible confounding factors; and the lower doses of smoke to which nonsmokers are exposed relative to smokers.

Let us examine these issues one by one. Are nonsmokers exposed to such low doses of environmental tobacco smoke (ETS) that Wells' estimates of 46 000 nonsmokers' deaths per year from passive smoking are about "46 000 too high", as Lee asserts? Perhaps the most salient point to be considered: active smoking is a cause of more than one out of every six deaths in the U.S.A. every year (USSG 1989). Intentional exposure to tobacco smoke has been judged to cause coronary heart disease, atherosclerotic peripheral vas-

cular disease, lung and laryngeal cancer, oral cancer, esophageal cancer, chronic obstructive pulmonary disease, chronic bronchitis, intrauterine growth retardation, and low birthweight babies. In addition, probable causality has also been established for unsuccessful pregnancies, increased infant mortality, and peptic ulcer disease, as well as cancers of the bladder, pancreas, and kidney, and associations have been reported for cancer of the stomach (USSG 1989). Hardly an organ system of the human body remains undiseased upon exposure to tobacco smoke. To argue, as do Lee and Katzenstein, that the diseases of smoking are not even plausible in nonsmokers does not give us confidence in their deductive abilities. To be sure, it is possible that thresholds for effect may exist for one or more of the diseases of smoking, but neither Lee nor Katzenstein present any evidence whatsoever that such low dose thresholds exist, let alone that all nonsmokers have exposures and susceptibilities which place them within an adequate margin of safety below such thresholds.

Are the epidemiological studies of passive smoking and lung cancer really all to be explained by misclassification of smokers as nonsmokers as Lee has proposed? Nonsmokers who report no passive smoking nevertheless possess levels of nicotine and cotinine in body fluids which are significant fractions of those who report a lot of exposure. For

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Let us examine these issues one by one. Are non-smokers exposed to such low doses of environmental tobacco smoke (ETS) that Wells' estimates of 46 000 nonsmokers' deaths per year from passive smoking are about "46 000 too high", as Lee asserts? Perhaps the most salient point to be considered: active smoking is a cause of more than one out of every six deaths in the U.S.A. every year (USSG 1989). Intentional exposure to tobacco smoke has been judged to cause coronary heart disease, atherosclerotic peripheral vas-

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example, of 100 nonsmokers studied by Jarvis (1987), the 46% who reported "no" exposure had measured urinary cotinine levels which were nearly a third of the levels of those 27% of nonsmokers who reported "some" or "a lot" of passive smoking exposure. This suggests that there is major misclassification of non-smoking controls as "unexposed". The result of this kind of misclassification of nonsmokers is to cause epidemiological studies to lack statistical significance or to find no effect. Nevertheless, despite such misclassification of controls, fully two-thirds of the studies shown by Katzenstein in his Table 1 showed a positive result.

Are confounding factors such as higher exposure to carcinogenic organic chemicals from non-ETS sources in the spouses of smokers, as Katzenstein asserts, really responsible for the consistent reports linking lung cancer to passive smoking from 15 different researchers in six different countries? To the contrary: Wallace (1989), in making measurements of personal exposure to benzene, a known human carcinogen and a prominent constituent of tobacco smoke, found that benzene exposures were 50% higher in the nonsmoking children and spouses of smokers than for nonsmokers in nonsmoking households.

Finally, what of the magnitude of Wells' (1988) estimates which Lee asserts are 46 000 too high? Let us take lung cancer, which Wells has estimated at 3000 U.S. lung cancer deaths (LCDs) per year. Lee selectively contrasts the estimate of 12 LCDs/yr from passive smoking by Arundel et al. (1987), but omits the mention of eight other risk assessments with which Wells' assessment agrees, all eight of which taken together average 5000 ± 2400 LCDs/yr. (Repace and Lowrey 1990). It is Arundel et al. who are out of step with the rest, not Wells. This lends credence to Wells' risk assessment methodology.

As far as heart disease mortality is concerned, this is primarily a disease of those aged ≥ 35 years. In 1985 there were roughly 105 million Americans in this age bracket, roughly 72 million nonsmokers, and 33 million smokers. Among the 33 million smokers, there were 120 000 active smoking-attributable heart disease deaths (HDDs) in 1985, or 3.6×10^{-3} HDD/smoker. By comparison, Wells' estimates 32 000 passive smoking-attributable nonsmokers' HDDs per year in a population of 72 million, or 4.4×10^{-4} HDD/nonsmoker. Thus, the ratio of ETS-induced heart disease deaths per nonsmoker to smoking-induced heart disease deaths per smoker is only 12%, which does not seem excessive considering that tobacco smoke is known to be one of three major risk factors for HDD, and synergistic (USSG 1989) with the other two fac-

tors (hypertension and elevated serum cholesterol) which are also common in nonsmokers.

A final note on Katzenstein's attack on the risks of passive smoking-induced lung cancer death (LCD) estimated by Repace and Lowrey (1985, 1986, 1987). The radical difference in lifestyle between never-smoking Seventh Day Adventist (SDA) controls and never-smoking non-SDAs is the avoidance of passive smoking in the SDA lifestyle, which we believe convincingly accounts for their lower lung cancer rate. As Katzenstein selectively notes, we were criticised by OTA (1985) and by tobacco industry consultants for attributing the entire LCD rate difference to passive smoking, but what our critics have conveniently ignored is that, since 60% of the SDA control group were potentially exposed to passive smoking, this was in fact a conservative estimate. Moreover, Katzenstein selectively omits mention of the analysis of our work by Weiss (1986), who found our figures to be "the best current estimates of lung cancer deaths from passive smoking".

In sum, contrary to the assertions of Lee and Katzenstein, we find Wells' predictions of 46 000 deaths per year from passive smoking to be credible, and to indicate, as Wells concluded, that exposure to ETS can have adverse long-term health effects that are more serious than previously thought.

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*The comments of the authors represent their opinions, and do not necessarily represent the policies of their respective federal agencies.

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AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING: A RESPONSE

Dear Editor:

An article in *Inside EPA* (January 13, 1989) is headlined: "EPA weighs Impact of Study Linking Passive Smoke Exposure to Heart Deaths . . ." It leads with the statement: "EPA is giving serious attention to a recently published study that pinpoints passive smoking . . . as a significant cause of heart disease and cancer-related deaths". The article states: "Passive smoking causes 46 000 deaths a year, according to a study by A. Judson Wells published last month in *Environment International*". An EPA source is quoted: "The 46 000 mortality was surprising because such a large component was from heart disease . . ." This statement is similar to one made by EPA's James Repace on national television when the report was first released.

What is surprising is that anyone from the EPA can consider this recent review surprising. Dr. Wells has not completed an epidemiological study, new or otherwise, and has in no way contributed to pinpointing passive smoking as a significant cause of heart disease, lung cancer, or other cancer deaths. What he did was publish the results of a series of calculations based on the results of existing epidemiological studies and a number of assumptions (Wells 1988). Dr. Wells presented a similar analysis at the 1986 Air Pollution Control Association meeting, which was published in the meeting proceedings (Wells 1986). There should have been no sudden surprise at EPA; an EPA official chaired the 1986 session in which this paper was presented. Dr. Wells encourages the view that he had done something new by failing to even acknowledge his previous presentation.

Wells used the data of previously published (and in some cases, unpublished) studies as a basis for calculating annual mortality statistically associated

with ETS exposure. These calculations do not in any way establish that ETS does, in fact, cause death in exposed individuals. Rather, such calculations rely on an independent conclusion, based on a review of the available data, that ETS causes lung cancer, other cancers, and cardiovascular diseases. If such a conclusion cannot be supported, then the estimate of ETS-associated mortality rests on the assumption that ETS causes these diseases, and it is incumbent upon the author to state this underlying assumption when reporting the results of his calculations.

The issue of causation is never addressed by Wells. The studies cited in Wells' Tables 1-4 are discussed below with particular attention to whether they establish a causal relationship between ETS and disease in non- or never-smokers. The vast majority of the studies were included in reviews published by the National Academy of Sciences (NAS 1986) and the Surgeon General (USSG 1986). Therefore, these reports are used as a starting point for addressing the question of causality.

Lung Cancer: Almost all of the epidemiological studies listed in Wells' Tables 1 and 2 were considered in the NAS and Surgeon General's reports, as well as other reviews appearing at about the same time (Blot and Fraumeni 1986; Überla 1987). The Surgeon General's Report was alone in concluding that ETS causes lung cancer in nonsmokers; the other reviews generally concluded that although a statistical association appeared to exist between marriage to a smoker and the risk of lung cancer, the lack of adequate exposure information, and the potential influence of differential misclassification of smoking status precluded a conclusion of causality. The lung cancer studies published since these reviews have the same limitations as the previous studies. Little has been published since 1986 that adequately addresses the issues of exposure and misclassification.

All of the studies attempting to link cancer to ETS have been epidemiological. An epidemiology study attempts to relate the frequency of a certain health effect or disease with the frequency of specific envi-

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ronmental exposures within a study group. Because of the nature of this type of study, all it can conclude is that the exposure and health effect do occur together with a measurable frequency. They do not prove a cause and effect relationship.

Koo et al. (1988) performed a detailed investigation of potential confounding factors in the lifestyle of nonsmoking women married to either a nonsmoking spouse or a smoking spouse. Overall, women married to ever smokers had a less healthy lifestyle, ate less vitamin A vegetables, ate more cured foods, ate more spicy foods, and drank more alcohol than women married to nonsmokers. Their analyses show that caution should be exercised when interpreting data on ETS without considering other factors.

Feinstein (1988) described some of the problems or failings that have come to characterize many epidemiological studies. Several examples are given where commonly used substances were accused of being a menace to daily life after epidemiologists reported a relatively weak association between use of the substance and adverse health effects. Some of these accusations have subsequently been refuted or withdrawn. Feinstein states that "[d]espite peer-review approval, the current methods need substantial improvement to produce trustworthy scientific evidence".

Other Cancers: With the exception of the Reynolds et al. study (which is unpublished and, therefore, inappropriately included in the analysis), all of the studies cited in Wells' Table 3 were included in the NAS and Surgeon General's reports. The NAS concludes that there is no consistent evidence, based on these studies, of any increased risk of ETS exposure for "cancers other than lung cancer". The Surgeon General's report similarly suggests that further investigation will be needed before any conclusion can be made.

Cardiovascular Disease: Wells suggests that a considerable body of new epidemiological data on ETS and cardiovascular disease has become available, which significantly impacts the analysis of data for this disease endpoint. This assertion is emphasized in the Inside EPA report. In fact, with the exception of Helsing et al. (1988), all of these data were available to the NAS and Surgeon General's review panels. The study of Martin et al. was available at the time but was unpublished, and for good reason, it thus was not cited in these reviews. The study remains unpublished, and the data should not be included in the present analysis.

Both the Surgeon General's and the NAS reports find the data on ETS and cardiovascular disease, available at the time of their reviews, to be inconclu-

sive. The inconclusiveness of the studies reflects not only small sample sizes but also a number of significant deficiencies in their design, as detailed in both the NAS and Surgeon General's reports. The questionable mathematical combination of the findings of these studies, as done by Wells, overcomes the problem of small sample size but in no way addresses the methodologic issues that have been raised.

The prospective study of Helsing et al. (1988) reports a statistically significant increased risk of death from cardiovascular disease in nonsmokers exposed to tobacco smoke in the home compared to those not so exposed. The authors of the study conclude that "[i]t seems reasonable to suppose that tobacco smoke is a risk factor in the increased risk". That rather weak conclusion reflects, in part, some aspects of the Helsing study that are inconsistent with such a conclusion. For example, the relative risk (RR) of death from heart disease associated with household exposure to ETS is reported as highest in the youngest age group studied (25-44 years old), even though the individuals in the older age groups presumably were exposed to ETS for much longer periods. Given the same estimate of household exposure, individuals in the older age groups would be expected to have had a higher risk of cardiovascular death than those in the younger group.

Both the Surgeon General's and NAS reports are cautious in their discussions of the quantitative risk associated with ETS exposure. Appendix D of the NAS report, which Wells cites in support of his risk models, emphasizes the underlying assumptions on which the calculations for lung cancer are based. The results are summarized in a section entitled, "Summary of Main Results Under the Assumption That the Summary Rate Ratio of 1.3 is Causal". The Surgeon General's report states (p. 96): "The quantification of the risk associated with involuntary smoking for the U.S. population is dependent on a number of factors for which only a limited amount of data are currently available". These factors include a better understanding of the magnitude of ETS exposure, its distribution among different segments of the U.S. population, and changes in the patterns of ETS exposure that have occurred over the last century. There is no better understanding of these factors now than there was in 1986. Wells bases his exposure estimates on data published by Friedman et al. (1983) — data that apparently were considered to be insufficient by the authors of the Surgeon General's report.

As Wells depended to a large extent on the Helsing (1988) report, it is important to review carefully the methodology used in that report. A general census

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was taken in Washington County, MD, in 1963 that included, among other factors, smoking histories of families and number of rooms in the house. Twelve years later, Helsing and colleagues reviewed death certificates to determine cause of death over the 12 years. They noted those deaths that were coded as arteriosclerotic heart disease and other myocardial degeneration. They then calculated a relative risk of death due to arteriosclerotic heart disease of nonsmokers married to smokers versus nonsmokers married to nonsmokers. The relative risks were 1.31 for men and 1.24 for women after adjusting for age, marital status, years of schooling, and quality of housing.

It is very important to note that the authors reported that there was a small difference in RR if heart disease was listed as the underlying cause of the death or just listed on the certificate as one of several reasons for death. The actual cause of death as listed on death certificates could in itself be a confounding factor in this study. In addition, overall relative risks were adjusted for age, marital status, etc. There is no description of how the quality of housing is calculated or adjusted for, nor is there any attempt to look at other possibly related health factors in the subpopulations to determine if these factors could have influenced arteriosclerotic heart disease. In addition, no attempt was made to measure smoking status misclassification.

Wells concludes his report by suggesting that exposure to ETS actually may cause more than 46 000 additional deaths per year. He quotes Repace and Lowrey (1985) and their estimate of 4665 additional lung cancer deaths as support for that suggestion. The Repace and Lowrey estimate scares a lot of people who have not taken the opportunity to review their underlying assumptions. What is overlooked in the emotionalism is what the Repace and Lowrey report really says.

Repace and Lowrey start with the assumption that direct smoking and ETS both cause cancer. They do nothing to prove this. They then use a long series of estimates of exposure concentrations and exposure durations to compare ETS exposure to direct smoking. Finally, they calculate the death rate from lung cancer using these assumptions and estimates. What they generate is a calculated guess, not a prediction based on facts.

Most of the research done since the Repace and Lowrey study has not supported its findings. One of the better studies has calculated that a person exposed to ETS actually retains 0.02 percent (or 1/5000)

of the particulates of a direct smoker (Arundel et al. 1988).

Repace and Lowrey calculate a nonsmoker to be exposed to an average of 1.43 mg/day of particulates from ETS. Arundel et al. calculated the amount to be 0.07 mg/day for male nonsmokers and 0.03 mg/day for female nonsmokers. These two estimates of ETS exposure differ by a factor of between 20 and 45. Thus, estimates based on exposure assumptions and models are simply estimates. One needs only to change a few of the basic premises to arrive at a completely different set of conclusions. Wells' reliance on assumptions derived from the exposure assumptions of Repace and Lowrey leave his own conclusions highly questionable.

It is apparent from this brief overview that Wells' computations rely on risk ratios derived from epidemiological studies that do not establish a causal link between ETS exposure and the risk of disease. What part, if any, of the association between marriage to a smoker and lung cancer or cardiovascular disease is due to ETS is a matter of debate. Resolution of that debate depends on further research to address the exposure and misclassification issues. Pending resolution of these questions, Wells is obligated to state and fully discuss the assumptions that underlie his calculations.

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AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING; A RESPONSE TO CRITICISM

Dear Editor:

Lee (1990), Katzenstein (1990), and Holcomb (1990) have commented negatively on my paper (Wells 1988a) in *Environment International*, in which it was suggested that the U.S. death toll from passive smoking may be 46 000 per year. Space does not allow me to deal with all of the points raised, but the more important ones are covered below.

Lee, as tobacco consultants usually do, attacks the underlying studies that I used, particularly the heart studies. I cannot speak for these authors. Dr. Hirayama has written a reply of his own. Dr. Sandler (private communication) has told me that they (Helsing et al. 1988) did look at family size and found no effect. The Johns Hopkins School of Public Health (Helsing et al. 1988) and the University of California, San Diego (Garland et al. 1985) are respected schools of epidemiology, whose researchers presumably know how to adjust for confounding variables. They attempted, within the limits of the data available, to account for known heart risk factors as noted in my paper. What is striking about the heart data in my Table 4 (Wells 1988a) is the consistency of the various results. It is interesting that Lee et al. (1986) made no attempt to adjust for any of the known heart risk factors except age.

Publication bias in smoking studies is an issue often raised by tobacco industry consultants, but so far no one has found a live passive smoking case that is negative. I have dealt with that issue vis-à-vis passive smoking and male lung cancer in my comment (Wells 1988b) on Vandenbroucke (1988). There, it was pointed out that the only available unpublished data were on the high side of the most probable relative risk, not low or negative. In that letter, I asked investigators to send me any data on passive smoking that had not been published or that they had

not been able to get published. So far I have received none. As Lee says, the possibility of a large, unpublished data set that found nothing cannot be excluded; it is just extremely unlikely.

For cancers other than lung that are passive smoking related, all except nasal sinus cancer and lung cancer are non-contact sites, as is heart disease. For these sites to be activated, the disease-producing entities must, in most cases, be metabolized and then circulate in the blood and lymphatic systems. Earlier work (Eatough et al. 1986) has shown that 90% of the nicotine in environmental tobacco smoke (ETS) is in the vapor phase. Now Pritchard et al. (1988) have shown that 70% of the tar in ETS is also in the vapor phase. The nicotine and the tar in direct smoking is in the particulate phase. It is true, as Lee says, that smokers are also passive smokers, but for the non-contact sites there is growing evidence that smokers have a higher risk if they are exposed to ETS other than their own than if they are not so exposed. For example, Palmer et al. (1988) found a relative risk for heart disease of 1.34 for spouse exposure of light smoking women and 1.32 for heavy smoking women, and Sandler et al. (1985) found overall cancer risks increasing from unity to 2.4 as active smokers were exposed to an increasing number of household members who smoked. This means that smokers may also be at considerable risk from passive smoking of their own smoke. In other words, for the non-contact sites, the vapor phase tar and nicotine may be the primary culprits, with the particulate phase having less effect. The particulate phase, at least most of it, is relatively quickly cleared. It probably contributes heavily to the contact sites (central lung, mouth, esophagus, and stomach) but then may be eliminated in the feces. All this means that Lee's model for passive smoking, which is based on direct smoking and particulate phase deposition and retention, is likely to predict relative risks for passive smoking that are far too low for the non-contact sites and probably for peripheral lung cancer as well.

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There are other factors that make the prediction of passive smoking health effects by rationing down from the particulate dose of direct smoking chancy. One factor is the possible protective effects in direct smoking. Smoking is known to depress estrogen levels which can protect against breast cancer. Such a protective effect is unlikely from passive smoking. Remmer (1987) postulates that direct smoking activates protective enzymes. Lassila et al. (1988), in their interesting work with monozygotic twins, have shown that direct smoking results in higher levels of prostacyclin, a reactive vasodilator, which, they note, could compensate for the vasoconstrictive effects of cigarette smoking. The dose from passive smoking is probably too low to promote this protective effect. Sinzinger et al. (1982), later confirmed by Burghuber et al. (1986) and Davis et al. (1989), found that platelet sensitivity, a known risk factor for heart attacks, is depressed about 30% in passive smokers, almost to the level found in active smokers. There is no way that the relative retained particulate dose could account for this phenomenon.

Direct smoking and passive smoking are both complex phenomena, with both disease promoting and disease protective components that differ between direct and passive smoking, and where the balance between them differs among individuals. Lee denigrates my suggestion that individual susceptibility could explain, in part, the higher than expected adverse health effects of passive smoking. The science of identifying highly susceptible people is progressing. See for example the work that Caparosa et al. (1989) are doing at the National Cancer Institute on "fast metabolizers" of potential carcinogenic materials. Jones (1986) has shown a substantial difference in sensitivity of different individuals to nicotine and its effect on pulse rate. Khoury et al. (1989) have developed equations for estimating the proportion of persons who are susceptible to a risk factor. They estimate that 13% of smokers are susceptible to lung cancer, whereas only 0.9% of smokers are susceptible to esophageal cancer. My calculations, using their formulae, indicate that only about 0.4% of nonsmokers are susceptible to death by lung cancer from passive smoking.

Lee says that I am "content to include all epidemiological studies" in my meta-analyses, regardless of quality. Actually, I discarded four lung cancer studies because they did not meet stated criteria. The admission criteria are admittedly broad because I did not wish to be accused of biased selection. Originally, I had intended to use only statistically significant data, but the meta-analysis technique allowed the inclu-

sion of smaller studies when properly weighted. A certain amount of scatter is to be expected and is observed in the relative risks from these smaller, low power studies.

Lee (1990) argues that the association between lung cancer and exposure to ETS arises predominantly because of bias caused by misclassifying smokers as nonsmokers. In his analysis he seems to have gone out of his way to stretch the data to fit his hypothesis. For example, he states that current typical regular smokers are misclassified to the extent of about 4%. In his workup (Lee 1986, 1987), he has confused smokers who say they are current non-users of tobacco with smokers who say they are never smokers. Yet the epidemiology of passive smoking deals almost exclusively with people who say that they are never smokers. Lee also averages male and female data in order to get higher misclassification factors. Normally in misclassification calculations, one uses sensitivity, which is defined as stated positives divided by stated positives plus false negatives, or in other words, the percent correctly classified as exposed, or in this case, the percent of ever smokers that are correctly classified as ever smokers. By basing his calculations on the number misclassified relative to never smokers instead of relative to ever smokers as he should have, he claims to be able to average male misclassifieds (who are mostly exsmokers) as 18% of self-reported never smokers with female misclassifieds as 6% of never smokers to yield a 10% misclassification factor. The misclassified males as 18% of never smokers are equivalent to only 6% of ever smokers ($18\% \times 25/75$) which is essentially the same as the female result ($6\% \times 50/50$). Of course the safe thing to do when estimating the bias in female passive smoking relative risks is to use only female data. In a paper in preparation for which I am a co-author, we found, when averaging data from five cotinine studies, including Lee's, that only 1% of female ever smokers said they were never smokers when they were actually current regular smokers, not 4% as Lee contends. Lee uses 10 as the observed relative risk for the regular current smokers that are misclassified as never smokers. The proper procedure is to use smoker relative risks that are consistent with the time frame and locale of the epidemiological studies for which a bias calculation is being made. Fortunately many of the passive smoking epidemiological studies on lung cancer have concurrent estimates of the relative risk of current or ever smokers, and values for the other studies can be estimated from available data. In fact, many of these values are shown on page 72 of Lee's book (1988). A

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log weighted average of the current smoker relative risk for the studies shown in Table 1 of my paper (Wells 1988a) is 4.56 (it was assumed that current smoker relative risk was 30% higher than ever smoker relative risk if those were the only data available) which is less than half the value of 10 used by Lee. Lee's book (1988) has whole sections devoted to misclassification factors for people who say they are recent exsmokers. These data appear to be introduced simply to confuse the reader since they have no bearing on passive smoking epidemiology which deals essentially entirely in self-reported never smokers. If proper factors are used for the extent of smoker misclassification and smoker relative risk, the bias that one calculates agrees with the values previously estimated by Wells (1986a, 1988a) and Wald et al. (1986), and not with those of Lee.

Lee suggests that my estimate of passive smoking deaths may be high. My heart relative risk of 1.23 is supported by two new studies and an update on a third. Palmer et al. (1988) report a female heart relative risk for passive smoking of 1.2, and Humble et al. (1990) report 1.6. Hole et al. (1989), in an update on the study of Gillis et al. (1984), report a female heart relative risk of 2.1 for low exposure passive smokers and 4.1 for high exposure. Sandler et al. (1989) found no increase in risk for total cancer in women, but Miller (1989) in his new study found that non-smoking, non-employed wives of nonsmokers accounted for only 3% of cancer deaths but a much higher percentage of total deaths. These two new results will offset each other. Sandler et al. (1989) also show a statistically significant female all cause relative risk of 1.15 for passive smoking, essentially identical to the 1.165 value I had derived in Appendix B (Wells 1988a) from earlier data. This tends to validate my estimate of 34 000 female all cause deaths from passive smoking. Sandler et al. (1989) also report a statistically significant all cause relative risk for men of 1.17 (the first such data available) that would result in 29 000 deaths per year for a total for both sexes of 63 000, higher than, but not too far distant from the 46 000 deaths that I estimated from the three-disease approach.

In our Western, non-traditional societies, it is very difficult to carry out these low-risk epidemiological studies because of the difficulty of finding a truly nonexposed reference category. Cummings et al. (1990) point out that 91% of the nonsmokers they interviewed had measurable cotinine in their urine while only 76% reported they had been exposed to tobacco smoke in the previous four days. Eighty-four percent of those not living with a smoker had measurable

cotinine. If these people are getting nicotine, known to be in the vapor phase of ETS, they must also be getting tar, now known also to be in the ETS vapor phase (Pritchard 1988). Miller (1989) has probably done the best job of ferreting out a nonexposed reference group with the result that he is finding very high relative risks for total cancer from passive smoking.

As Goldstein (1986) has said, "Chemicals shown to be carcinogenic are considered by regulators as 'guilty until proven innocent' of having no threshold. This conservative approach essentially puts the burden on the producer or user of providing the scientific evidence justifying a threshold in regulating a carcinogen." The purpose of my paper was to provide regulators with an estimate of the most probable death toll from passive smoking given the existing epidemiological evidence, and also data from which to calculate an upper bound estimate, as they usually wish to do. Nothing in Lee's comments, with his botched bias analysis and his flimsy dose model, does anything to "justify a threshold" for this known human carcinogen.

Katzenstein (1990) also appears to be very selective in the data that he reports in Table 1 of his letter and he does not appear to have done his homework in finding all the reports on passive smoking and lung cancer that have issued since the 1986 reports of the National Academy of Sciences (NRC 1986) and the Surgeon General (USSG 1986). Commenting first on the reports that he lists, Chan and Fung (1982) is simply a restatement of the more detailed data in Chan et al. (1979). I had rejected Chan et al. (1979) and Dalager et al. (1986) for reasons stated in my paper. Dalager's crude relative risk of 1.00 that Katzenstein reports is for both sexes. The only female all exposure relative risk in that paper is 1.96 for spouse exposure, not statistically significant. However among older women, 63 plus years of age, with high intensity exposure, the odds ratio was 5.14 with 95% confidence limits of 1.4 to 18.95. A dose response trend was also observed. Kabat et al. (1984) found a statistically significant odds ratio of 3.3 for male exposure at work and also found a statistically significant Mantel test for linear trend in the frequency of exposure (four levels) for males ($p < 0.005$). Garfinkel et al. (1985) had a statistically significant odds ratio of 2.0 at the highest exposure. The results that Katzenstein quotes from Gao et al. (1987) are for never smoking women who ever lived with a smoker. For spouse exposure they report a rising relative risk from 1.0 for less than twenty years exposure to a statistically significant 1.7 for forty

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plus years exposure. Shimizu et al. (1988), besides reporting the 1.1 nonsignificant risk for nonsmoking wives exposed to a husband's smoke also report a 4.0 significant risk for exposure to a mother's smoking and 3.2 for exposure to the husband's father's smoking. The latter is not unusual since wives in Japan, after they leave their mother's home, often live with the husband's family and the husband's father is often retired. Wu et al. (1985), Brownson et al. (1987), Humble et al. (1987), and Lam et al. (1987) were covered in my paper (Wells 1988a). The male relative risk in Humble et al. (private communication) is a statistically significant 4.2. New reports that Katzenstein evidently is not aware of are (1) the Hong Kong thesis of W. K. Lam (1985) with 60 female cases and a statistically significant relative risk of 2.01 and a risk for peripheral tumors of 2.64 ($p < 0.05$); (2) Geng et al. (1988) with 54 cases and a statistically significant odds ratio of 2.16 for all levels of exposure, and 2.76 with 95% confidence limits of 1.85 to 4.10 for exposure to 20 plus cigarettes per day. They also report a relative risk from ETS for smoking wives of 1.88; (3) Inoue and Hirayama (1988) with 22 cases report a nonsignificant odds ratio of 2.25 for all exposure levels, but for exposure to 20 plus cigarettes a day the odds ratio is a statistically significant 3.35 (they also report a statistically significant positive trend); (4) Svensson (1988), in a thesis from Sweden, with 34 female nonsmoking lung cancer cases, found a relative risk of 1.2 for exposure at home or at work and a relative risk of 2.1 for exposure at home and at work. He also found a relative risk of 1.4 for exposure as a child or as an adult and 1.9 for exposure both as a child and as an adult. None of Svensson's relative risks is statistically significant; and (5) Varela (1987) also in a thesis, this one from Yale University, reports on 218 female cases and 221 male cases which included both never smokers and long-term exsmokers. He found no increase in risk for spouse exposure or workplace exposure but found a statistically significant relative risk of 1.87 multiple exposures at home.

Katzenstein's attack on the underlying studies is a typical tobacco industry approach. As we know, all epidemiological studies are flawed to one extent or another. However the National Academy and the Surgeon General, looking at the totality of the studies then available, concluded that passive smoking can cause lung cancer, and inclusion of the studies new since 1986 would not change that conclusion.

Katzenstein is wrong when he says that the heart studies failed to consider cardiovascular risk factors. Garland et al. (1985) and Helsing et al. (1988) ad-

justed for several of them. The Svendsen study (1987) considered ten of the most frequently studied heart risk factors, comparing 286 nonsmoking men married to smokers and 959 married to nonsmokers. The differences were small, and adjusting for them did not decrease the observed risk. Katzenstein quotes an American Cancer Society 1988 release saying that currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers. He must have found this in the rare book store since neither the Delaware office nor the national office of the American Cancer Society could find this reference. On the contrary the ACS "Cancer Facts and Figures for 1989" states that involuntary smoking increased the risk of lung cancer, and their "The Smoke Around You" pamphlet issued in 1987 quotes the 35% increase in lung cancer risk for passive smoking that is found in the National Academy report (NRC 1986).

In Katzenstein's "final comment" where he quotes the NAS and USSG reports on passive smoking and heart disease, he fails to note that the best heart evidence is in papers issued since those reports came out. It is interesting that the newest reports (Palmer 1989; Hole 1989; Humble 1990) all support a positive relative risk.

Holcomb (1990) states that I had encouraged the view that the results in Wells (1988a) were new. Actually that paper has a long history. The original version was presented at a seminar at the Harvard School of Public Health in December, 1984. An update was presented to the National Research Council in January, 1986. The version Holcomb refers to was presented at the June, 1986, meeting of the Air Pollution Control Association, and in September, 1986, before the Natural Resources, Agriculture Research and Environment Subcommittee of the Committee on Science and Technology of the U.S. House of Representatives. It is published in the proceedings of those meetings (Wells 1986b, 1987). After extensive revision, a shortened version was presented at the 6th World Conference on Smoking and Health in Tokyo in November of 1987. A summary is published in the proceedings of that meeting (Wells 1988c). The first draft of the current version (Wells 1988a) contained a summary of this history, but the editors of *Environment International* decided that since none of the earlier versions had been adequately peer reviewed, reference to them could be omitted. It should be noted that the current paper profited by the many comments received over the years from many experts in the field who either commented gratuitously or whose advice was solicited. James Repace was sur-

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prised in 1986 at the large number of heart deaths and is probably still surprised, as are many others, but that is the way the numbers come out.

Holcomb states that I did not address the issue of causation. Perhaps this should have been done more explicitly in the paper. It was pointed out on the first page of the paper that the Surgeon General's report (USSG 1986) and the National Academy report (NRC 1986) both stated that passive smoking can cause lung cancer. I thought that was adequate coverage for that issue. (Incidentally Holcomb states that "the Surgeon General's report was alone in concluding that ETS causes lung cancer in nonsmokers," but on page 10 of the National Academy report it is stated, "Considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers.") Then I went on to show that the heart data, including the new data, had most of the same characteristics as the lung cancer data in terms of number of cases, statistical significance, dose response, and biological plausibility. Hence one could infer causation.

Holcomb references a paper by Koo et al. (1988) that allegedly shows that nonsmoking women married to ever smokers had a less healthy life style than nonsmoking women married to nonsmokers. Careful analysis of their voluminous data indicates eight life style factors where the test p and the p for trend were both reasonably small. Five indicated a healthier life style for the women married to the never smokers and three for those married to the smokers. About all this paper shows is that nonsmoking women in Hong Kong who lived in rural areas are more likely to be married to nonsmokers and to have a more rural life style. Humble et al. (1990), in their soon-to-be-published paper on passive smoking among never smoking women in Georgia, found that higher social status white women had a higher relative risk of heart disease from ETS than lower social status white women, quite the reverse from what Koo et al. concluded. Humble et al. also adjusted for age, diastolic blood pressure, total serum cholesterol, and body mass. The tobacco people have used misclassification as their principal smoke screen to discredit lung cancer risk from passive smoking. They know that misclassification can't possibly explain the heart effects of passive smoking so they have embraced "life style". This also is proving to be ephemeral.

Holcomb complains that I included unpublished studies in the analysis, but Katzenstein complains that publication bias is likely to omit pertinent data. I chose to include all the data I knew about,

favorable or unfavorable. Omission of the unpublished studies would not change the conclusions.

Holcomb states that I based my exposure estimates on data published by Freidman et al. (1983). Actually, the exposure of never smokers living with ever smokers was obtained from the exposure of controls reported in the various U.S. passive smoking studies. This represents the major factor in female exposure. Only the exposure of nonsmokers living with nonsmokers was estimated using Friedman et al.

There is no question that my conclusions on heart disease and cancers other than lung go further than the cautious statements in the Surgeon General and National Academy of Science reports. So far, however, the new data support my position. Whether causation has been "proved" or not, public health officials need to know the mortality stakes involved. They can then make their own judgments as to the likelihood of causality.

Holcomb has not read the paper of Repace and Lowrey (1985) carefully. Their estimate of 4665 lung cancer deaths from passive smoking is based on a comparison of lung cancer mortality rates of Seventh Day Adventists who never smoked with those of non-Seventh Day Adventists who never smoked, not on exposure estimates as Holcomb claims. My estimates in no way rely on the exposure estimates of Repace and Lowrey. There are some nine studies in the literature that estimate lung cancer deaths from passive smoking. Except for Arundel et al. (1987) estimate, they range from 600 to 5600. The Arundel estimate is based on extrapolation from smokers to nonsmokers of retained particulate dose, an idea discredited earlier in this letter.

As Katzenstein says, death from passive smoking is a serious issue, serious to the health of the tobacco industry, and serious to the public health. We can expect vigorous (but misleading) attacks from the tobacco side, as these three letters show, but it is still best to lean toward safety when the health of the public is at stake.

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Deaths from lung cancer and ischaemic heart disease due to passive smoking in New Zealand

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Abstract

Passive smoking is increasingly recognised as a public health hazard. Among New Zealanders who have never smoked, the prevalence of exposure to spousal smoking has been estimated to be 12.7% for men and 16.1% for women. The prevalence of exposure to passive smoking in the workplace has been estimated to be 33.6% and 23.4% for never smoking men and women respectively. The pooled risk estimates from epidemiological studies of the health effects of passive smoking were used to estimate the numbers of deaths from lung cancer and ischaemic heart disease attributable to passive smoking in New Zealand in 1985. The pooled relative risk estimates for lung cancer mortality were 1.3 (95% confidence interval (CI): 1.1-1.5) in both men and women exposed to passive smoking at home, and 2.2 (CI 1.4-3.0) in both men and women exposed to passive smoking at work. Using these relative risk estimates, it was calculated that 30 lung cancer deaths (range: 11-41) were attributable to involuntary smoking in New Zealand in 1985.

From pooled relative risk estimates of ischaemic heart disease death of 1.3 (CI 1.1-1.6) and 1.2 (CI 1.1-1.4) for exposure to spousal smoking in men and women respectively, it was estimated that a further 91 ischaemic heart disease deaths (range: 39-177) were due to passive smoking at home. The number of ischaemic heart disease deaths due to passive smoking in the workplace was even higher, at 152 (range: 62-224), assuming relative risks of 2.3 (CI 1.4-3.4) and 1.9 (CI 1.4-2.5) for men and women respectively.

The total number of deaths due to passive smoking from lung cancer and ischaemic heart disease was therefore estimated to be 273 per year (range: 112-442).

publication, has been put forward as an explanation for the association between passive smoking and lung cancer [10]. However, this claim has been criticised and discredited [11]. More recently, evidence has begun to accumulate which implicates passive smoking in the development of ischaemic heart disease [12-14].

Passive smoking is therefore a potentially important public health problem in New Zealand, and it is desirable to assess the magnitude of the problem. Taking the relative risk estimates reported in epidemiological studies and applying them to estimates of the proportion of the New Zealand population exposed to passive smoking, we have made a preliminary estimate of the impact of passive smoking on the health of nonsmokers.

We here report estimates of the numbers of deaths from lung cancer and ischaemic heart disease attributable to prolonged exposure to passive smoking in New Zealand in 1985. The evidence of excess deaths from other causes - i.e. cancers of sites other than the lungs, and chronic respiratory disease - due to passive smoking is more tenuous [2]. Death from these causes has therefore not been considered here.

Statistical methods

The proportion of deaths from a particular disease attributable to a specific exposure is known as the population attributable risk (also referred to as the etiologic fraction).

If p is the proportion of the general population exposed to the risk factor (in this case involuntary smoking) and RR is the relative risk of dying of the disease in exposed versus nonexposed individuals, then the population attributable risk is given by [15]:

$$PAR = \frac{p(RR - 1)}{p(RR - 1) + 1}$$

This measure has been used in many previous studies, including two studies which estimated the proportion of deaths in New Zealand attributable to active smoking [16,17], as well as in a Canadian study which estimated the proportion of lung cancer deaths attributable to passive smoking [8].

In the current study, the relative risk estimates from overseas studies were applied to New Zealand data on passive smoking exposure, and the derived population attributable risks were then applied to lung cancer and ischaemic heart disease deaths in 1985 among persons who had never smoked [18]. The population attributable risks and deaths attributable to passive smoking were estimated separately for men and women, and for exposure at home and at work.

Estimation of exposure to passive smoking

Estimation of exposure to passive smoking at home: Estimates of the prevalence of exposure of never smokers to passive smoking at home were obtained from the Auckland heart study (work in progress). The study found that 12.7% of never smoking men and 16.1% of never smoking women aged 35-64 years in Auckland in 1987-88 were exposed to passive smoking in their homes. These figures are not limited to exposure to spousal smoking, but include exposure to all

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Introduction

Recent reviews have concluded that exposure to passive smoking is harmful to health [1-4]. The effects of passive smoking on health have been reported to include acute effects, such as exacerbation of asthma and angina, as well as chronic effects such as the increased risk of upper and lower airways infection in children and the increased risk of lung cancer in adults [4].

The association of lung cancer with passive smoking appear to satisfy epidemiological criteria of causality [5,6]. To date 13 studies have been completed in six countries, 10 of which have reported a positive association between lung cancer and passive smoking [6]. Three studies have failed to show an association [7-9], but in each study the precision of the effect estimates was such that an increased risk could not be ruled out. Publication bias, i.e. bias which occurs when papers with nonsignificant results are either not submitted or accepted for

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other sources of passive smoking within the household. On the other hand these figures are likely to underestimate the effects of long term exposure to spousal smoking, since we have not taken account of never smokers who have been previously exposed to passive smoking, but are currently widowed, separated, divorced, or living with exsmokers.

Estimation of exposure to passive smoking in the workplace: The prevalence of exposure to passive smoking in the workplace was also obtained from the Auckland heart study. In this study, 33.6% and 23.4% of never smoking men and women, aged 35-64 years in Auckland in 1987-88, were exposed to passive smoking at work. A recent random telephone survey of the Wellington region reported that the proportion of nonsmokers exposed to passive smoking in the workplace may be even higher, reaching up to 80% (19). However a significant proportion of the respondents reported that most of their exposure occurred during tea and lunch breaks. Therefore we adopted the more conservative prevalence estimates.

Estimation of relative risks associated with exposure to passive smoking

Estimation of the relative risk of lung cancer due to passive smoking at home: The relative risk of dying of lung cancers in never smokers exposed to spousal smoking was obtained from the pooled results of 10 case control studies and two prospective studies (20). The relative risk of lung cancer mortality in women who had never smoked and who were married to ever smokers, weighted by the Mantel-Haenszel procedure, was 1.3 (95% confidence interval: 1.1-1.5) (20). There have been few studies of lung cancer among men who have never smoked. We have assumed, as others have done (6), that the relative risk of lung cancer in never smoking men married to ever smoking women is the same as for never smoking women married to ever smoking men (Table 1).

Table 1. — Estimates of relative risk of deaths from lung cancer and ischaemic heart disease due to passive smoking (95% confidence interval)

Disease	Relative risk from exposure at home		Relative risk from exposure at work	
	Men	Women	Men	Women
Lung cancer	1.3 (1.1-1.5)	1.3 (1.1-1.5)	2.2 (1.4-3.0)	2.2 (1.4-3.0)
Ischaemic heart disease	1.3 (1.1-1.6)	1.2 (1.1-1.4)	2.3 (1.4-3.4)	1.9 (1.4-2.5)

Estimation of the relative risk of lung cancer due to passive smoking in the workplace: The elevated lung cancer risk from passive smoking has been well established, but few studies have specifically examined risks from workplace exposures. Thus instead of using direct estimates, the relative risk for lung cancer death from exposure to passive smoking in the workplace was estimated via an exposure response relationship derived by Repace and Lowrey (8,21). They estimated that the degree of exposure to passive smoking at home, at work, and at both sites, corresponded to respective daily inhalation of 0.45, 1.82 and 2.27 mg of the particulate phase of ambient tobacco smoke (8). According to this model, exposure to passive smoking at work should result in a higher risk for lung cancer than exposure at home. Based on the relative risk estimate of 1.3 for home exposure (Table 1), the relative risk of lung cancer in persons exposed to passive smoking in the workplace was estimated to be 1.4 (0.3 x 1.82/0.45), yielding a relative risk estimate of 2.2 (range: 1.4-3.0) (Table 1). This estimate is consistent with the relative risk of 3.3 (95% confidence interval: 1.0-10.5) for never smokers exposed to passive smoking at work reported by Kabat and Wynder (22), in one of the few studies that has distinguished exposure at work from exposure at home. However, we have adopted the more conservative estimate of 2.2 (Table 1).

Estimation of the relative risk of ischaemic heart disease death due to passive smoking at home: The estimates for the relative risk of ischaemic heart disease death in never smokers exposed to spousal smoking were obtained from Wells' pooled analysis

of five cohort studies and two case control studies (23). The pooled relative risk for men exposed to spousal smoke, weighted by the Mantel-Haenszel procedure, was 1.3 (CI: 1.1-1.6), and the corresponding estimate for women was 1.2 (CI: 1.1-1.4) (23).

Estimation of the relative risk of ischaemic heart disease death due to passive smoking in the workplace: There is at present scant data on the relative risk of ischaemic heart disease death due to passive smoking in the workplace. The study by Svendsen et al (13), based on data from the MRFIT trial, reported that the relative risk of coronary heart disease death in men exposed to coworkers' smoke compared with men whose coworkers did not smoke, was 2.6 (13). However, the risk estimate was imprecise (CI: 0.5-12.7; p=0.23), and in addition, the MRFIT trial involved men who were at high risk of coronary heart disease at entry.

Nevertheless, a higher value for the relative risk of ischaemic heart disease death from exposure to passive smoking in the workplace compared to the home is consistent with the greater prevalence and intensity of exposure obtained in the former setting (8). Using the same assumptions as in our calculation of the relative risk of lung cancer from passive smoking in the workplace, we estimated that the relative risk of ischaemic heart disease death from passive smoking in the workplace was 2.3 (range: 1.4-3.4) for men and 1.9 (range: 1.4-2.5) for women, respectively (Table 1).

Estimation of deaths due to passive smoking

There are a considerable number of uncertainties in the estimation of deaths due to passive smoking in New Zealand. These relate to uncertainties in the number of deaths in never smokers, the prevalence of exposure to passive smoking, and the relative risks due to passive smoking. The main uncertainty stems from the relative risk estimates. Accordingly, to provide a range of plausible values for the population attributable risks, the 95% confidence interval for the relative risk estimates (Table 1) have been used, and the other estimates have been regarded as fixed. Ranges have also been provided for the estimates of the number of deaths in never smokers (Tables 2-5) in order to give an indication of their precision, but these ranges have not been used in further calculations.

Estimation of lung cancer deaths attributable to passive smoking at home: In 1985 there were 1197 lung cancer deaths in New Zealand (18) — 866 in men and 331 in women. It was estimated from the cancer registry data that 8% of these deaths occurred in never smokers (24). Therefore 69 male lung cancer deaths, and 26 female lung cancer deaths occurred in never smokers (Table 2).

Table 2. — Estimated number of deaths from lung cancer attributable to passive exposure to spousal smoke in New Zealand in 1985, by sex

	Men	Women
Total no of lung cancer deaths	866	331
% of people who had never smoked	8%	8%
No of lung cancer deaths in those who had never smoked	69	26
Prevalence of never smokers exposed to spousal smoking	12.7%	16.1%
Relative risk of lung cancer for exposure to spousal smoke (CI)	1.3 (1.1-1.5)	1.3 (1.1-1.5)
PAR, spousal smoke (range)	3.7% (1.3-6.0%)	4.8% (1.6-7.5%)
No of lung cancer deaths in never smokers attributable to spousal smoking (range)	3 (1-4)	1 (0-2)

PAR = population attributable risk

The population attributable risks were calculated to be 3.7% (range: 1.3-6.0%) for men, and 4.8% (range: 1.6-7.5%) for women (Table 2). The numbers of lung cancer deaths in 1985 attributable to passive smoking at home were therefore estimated to have been 3 (range: 1-4) for men and 1 (range: 0-2) for women, giving a total of 4 (range: 1-6).

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Estimation of lung cancer deaths attributable to passive smoking in the workplace: Assuming a relative risk of 2.2, the population attributable risk for lung cancer deaths due to passive smoking in the workplace is 28.7% (range: 11.8-40.2%) for men, and 21.9% (range: 8.6-31.9%) for women (Table 3). The number of lung cancer deaths in never smokers attributable to passive smoking in the workplace is therefore estimated to have been 20 (range: 8-28) for men, and 6 (range: 2-7) for women, giving a total of 26 (range: 10-35) (Table 3).

The total annual number of lung cancer deaths attributable to passive smoking is thus estimated to have been 30 (range: 11-41), of which 87% is attributable to exposure in the workplace.

Table 3 - Estimated number of deaths from lung cancer attributable to passive smoking in the workplace in New Zealand, 1985, by sex

	Men	Women
No of lung cancer deaths in never smokers	69	26
Prevalence of exposure to passive smoking in never smokers who work	33.6%	23.4%
Relative risk of lung cancer for exposure to passive smoking at work (CI)	2.2 (1.4-3.0)	2.2 (1.4-3.0)
PAR, work exposure (range)	28.7% (11.8-40.2%)	21.9% (8.6-31.9%)
No lung cancer deaths in never smokers attributable to passive smoking at work (range)	20 (8-28)	6 (2-7)

PAR = population attributable risk

Deaths from ischaemic heart disease attributable to passive smoking at home: Data on the proportion of ischaemic heart disease deaths occurring in never smokers in New Zealand were not available. We estimated this proportion by applying the relative risks of ischaemic heart disease death - obtained from the cohort study by Doll and Peto (25,26) - for each category of smoking (never smoked, ex-smoker, smoking between 1-14, 15-24, and over 25 cigarettes per day) to the proportions of New Zealanders aged over 25 years in each category, based on the 1981 census data (27). The proportions of never smokers among ischaemic heart deaths were then calculated as the percentage of all ischaemic heart disease deaths that would be expected to occur, based on these relative risks. It was thus estimated that 32.3% and 42.0% of ischaemic heart disease deaths occur in male and female never smokers, respectively. These figures are in close agreement with unpublished data from a coronary heart disease register in Auckland (Jackson R; work in progress).

The population attributable risks for ischaemic heart disease deaths in persons exposed to spousal smoke were estimated to be 3.7% (range: 1.3-7.1%) in men, and 3.1% (1.6-6.1%) in women (Table 4). The number of ischaemic heart disease deaths attributable to passive smoking in the home is estimated to have been 51 (range: 18-97) in men, and 40 (range: 21-80) in women, a total of 91 deaths (range: 39-177).

Table 4 - Estimated number of deaths from ischaemic heart disease attributable to passive exposure to spousal smoking in New Zealand, 1985, by sex

	Men	Women
Total no of deaths from IHD	4234	3108
% of people who had never smoked	32.3%	42.0%
No of people who had never smoked	1368	1305
Prevalence of exposure to spousal smoke among married never smokers	12.7%	16.1%
Relative risk of IHD for exposure to spousal smoke (CI)	1.3 (1.1-1.6)	1.2 (1.1-1.4)
PAR, spousal smoke (range)	3.7% (1.3-7.1%)	3.1% (1.6-6.1%)
No of IHD deaths in never smokers attributable to spousal smoking (range)	51 (18-97)	40 (21-80)

PAR = population attributable risk; IHD = ischaemic heart disease

Deaths from ischaemic heart disease attributable to passive smoking in the workplace: Since the risk of ischaemic heart disease from active smoking diminishes rapidly after cessation of smoking, it was assumed that the risk of ischaemic heart disease death from exposure to passive smoking in the workplace would similarly decline after withdrawal from the workforce. Furthermore, the estimates of workplace exposure used in this study (Tables 3 and 5) were based on data for Aucklanders aged 35-64 years. Thus, conservative estimates of ischaemic heart disease deaths due to exposure to passive smoking in the workplace were derived from the number of ischaemic heart disease deaths which occurred among those of working age, i.e. those aged under 65 years. In this age group there were 1276 deaths in men and 366 in women in 1985 (18) (Table 5).

Table 5 - Estimated number of deaths from ischaemic heart disease attributable to passive smoking in the workplace in New Zealand in 1985

	Men	Women
Total number of ischaemic heart disease deaths in people aged <65 years	1276	366
% of people who had never smoked	32.3%	42.0%
Number of ischaemic heart disease deaths in never smokers aged <65 years	412	154
Prevalence of exposure to passive smoking in never smokers who work	33.6%	23.4%
Relative risk of ischaemic heart disease from exposure to passive smoking in the workplace (CI)	2.3 (1.4-3.4)	1.9 (1.4-2.5)
PAR, workplace exposure (range)	30.4% (11.8-44.6%)	17.4% (8.6-26.0%)
No of ischaemic heart disease deaths in never smokers attributable to smoking in the workplace (range)	125 (49-184)	27 (13-40)

PAR = population attributable risk

The population attributable risks for deaths from ischaemic heart disease due to passive smoking in the workplace, assuming relative risks of 2.3 for men and 1.9 for women, were 30.4% (range: 11.8-44.6%) in men, and 17.4% (range: 8.6-26.0%) in women. These yielded estimates of 125 (range: 49-184) ischaemic heart disease deaths in men, and 27 (range: 13-40) deaths in women, a total of 152 deaths (range: 62-224) (Table 5).

Discussion

The estimated total of 30 lung cancer deaths attributable to passive smoking represents 2.5% of all lung cancer deaths in 1985, and 31.6% of lung cancer deaths in those who had never smoked. These results are similar to previous estimates for USA (6) and Canada (5). Repace and Lowrey estimated that passive smoking was responsible for 5% of the total annual lung cancer deaths, and 30% of the lung cancer deaths in never smokers in the USA (6). Wigle and Collishaw estimated that in Canada passive smoking was responsible for 2.3% of the total annual lung cancer deaths, and 51% of lung cancer deaths in never smokers (5).

It is estimated that 243 deaths from ischaemic heart disease occurred in 1985 due to passive smoking. This represents 3.3% of all ischaemic heart disease deaths, and 9.1% of ischaemic heart disease deaths in never smokers. The total number of deaths in New Zealand in 1985 from lung cancer and ischaemic heart disease due to passive smoking was estimated to have been 273 (range: 112-442), of which 65.2% was attributable to exposure in the workplace (Table 6).

As we have stressed throughout, there are a number of uncertainties in these calculations, and the total of 273 deaths per year from lung cancer and ischaemic heart disease due to passive smoking should be regarded as only a preliminary estimate. Nevertheless it does indicate the likely magnitude of the mortality due to passive smoking in New Zealand. The findings of this study will need to be revised as more accurate data, particularly on the relative risks of diseases due to workplace exposure to passive smoking, become available.

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However there are a number of reasons to suggest that the figures presented here are underestimates. Firstly, we have not considered the numbers of deaths attributable to passive smoking in two groups of nonsmokers: (1) never smokers who are not currently exposed to passive smoking at home (and in the case of ischaemic heart disease cases, at work), but who have been exposed in the past, and (2) exsmokers currently exposed to passive smoking. Secondly, we have not considered exposure to passive smoking in situations other than at home or at work, nor the impact of passive exposure to pipe or cigar smoking. Thirdly, we have not made adjustments to the relative risks for possible misclassification of exposures. In studies which have corrected for these biases (23,28), the net effect of the adjustment was to raise the relative risk estimates. Fourthly, we have not attempted to estimate the numbers of deaths from cancers of sites other than the lungs. Based on three cohort and two case control studies, Wells estimated that the relative risk of cancers other than the lungs in never smoking women exposed to passive smoking was 1.16 (95% confidence limits: 1.06-1.27) (23). Excess cancers were observed for cancers of the breast, cervix, brain, paranasal sinuses and endocrine glands (23). Although these studies have been criticised for their failure to control for risk factors known to be associated with cancers of these sites (2), it is nevertheless likely that at least some deaths from these cancer types are attributable to passive smoking. Finally, we have not attempted to estimate the numbers of pneumonia deaths attributable to passive smoking in childhood, nor the increased numbers of perinatal deaths associated with smoking during pregnancy (4).

Despite the uncertainties in the estimates presented here, they nevertheless suggest that passive smoking is a major public health problem in New Zealand. Although a more precise estimate of the number of deaths due to passive smoking must await further studies, there is a clear case for taking action on current evidence. The protection of the health of nonsmokers, particularly in the workplace and in enclosed public places, must be given priority as an issue of environmental health protection. It is encouraging that the necessary regulatory actions are beginning to occur.

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Congenital long QT syndrome in adults

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Abstract

A family with the Romano-Ward syndrome is presented. This family showed typical features of this syndrome with QT prolongation, torsades de pointes ventricular tachycardia, sudden death and an autosomal dominant inheritance pattern. The index case presented with an exacerbation of torsades de pointes ventricular tachycardia from diuretic induced hypokalaemia, and responded to diuretic withdrawal and beta blocker therapy.

NZ Med J 1988; 102: 340-1

Introduction

Abnormalities of ventricular repolarisation predispose the heart to ventricular arrhythmias, typically polymorphic ventricular tachycardia (torsades de pointes). Abnormal repolarisation is typically represented on the surface electrocardiogram by QT interval prolongation. However T

or U wave abnormalities may also reflect abnormal repolarisation. Abnormal repolarisation is usually acquired due to cardiac injury, metabolic derangement or drugs. Rarely, abnormal repolarisation is congenital and may occur either sporadically or as an autosomal recessive or dominant condition.

We present a family with autosomal dominant QT prolongation and torsades de pointes ventricular tachycardia.

The patient

The index case was a 44 year old female with a life long history of syncope which was usually precipitated by exertion or emotional stress. Three months prior to admission she was commenced on cyclophosphamide 0.5 mg daily for hypertension. Since commencement of cyclophosphamide she reported that the syncopal episodes became more frequent and prolonged. During one episode she was observed by her husband to be pale and pulseless. She had no other significant past history, and was on no other medications. On admission to hospital she was anxious but otherwise well. Blood pressure was 140/80 mmHg and general examination normal. Resting rhythm strip

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What is of greater concern is the way in which your correspondents have sought to obscure the message of our paper. This message is that patients in our study were unhappy about charges which had inflated at 24% per annum. No amount of analysis of the total fee, of GST or of general practitioner incomes will change these facts. Nor will they be altered by claims that patients have no right to determine what they deem to be a fair and reasonable cost for medical care.

Further, some of your correspondents imply that the purpose of our paper was to criticise general practice and to bring general practitioners into disrepute. This is not so, as will be seen from our previous article (1) on this topic. The purpose of the present article was not to denigrate the efforts of general practitioners but rather to bring to attention a current public perception of the cost of their services. We would hope that this evidence will contribute positively to policy attempts to devise a fee structure which ensures that family doctors receive a fair return for their efforts while at the same time protecting patients from the current inflation in patient charges which has largely been caused by the way in which the relationships between the total fee and GMS are set.

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1. Fergusson DM, Beutrais AL, Shannon FT. Maternal satisfaction with primary health care. NZ Med J 1981; 94: 291-4.

Deaths from lung cancer and ischaemic heart disease due to passive smoking in New Zealand

Kawachi, Pearce and Jackson (1) estimate that passive smoking causes 273 deaths per year in New Zealand, 30 from lung cancer and 243 from ischaemic heart disease (IHD). Some 65% of these deaths are attributed to workplace exposure, the rest to spousal smoking. These estimates are scientifically unjustified. Too much weight is given to fragile epidemiological data, major sources of bias being totally underestimated. Too little weight is given to evidence that nonsmokers have very low exposure to tobacco smoke constituents.

The evidence that passive smoking increases risk of IHD is very unconvincing. The authors (1) cite a meta-analysis by Wells (2) for their estimate of risk in relation to spouse smoking. This is based on 7 studies, many of which involve unacceptably small numbers of cases, eg, as low as two deaths in women married to never smoking husbands (3). The two studies with adequate numbers are both open to question.

One of these is the Japanese prospective study (4,5). Wells cited results from 17 years follow up (5) which claimed a significant trend in IHD in relation to spouse smoking, but failed to mention that this finding significantly ($p < 0.001$) conflicted with an earlier report, based on 14 years follow up which claimed no association whatsoever!

The other is the Maryland prospective study (6) which reported 34% and 24% increases in IHD in men and women in relation to spouse smoking. This study has many features that are noteworthy. It made no attempt to follow up people moving outside Washington County, thus missing large numbers of deaths. It found no dose response relationship. It failed to collect data on a whole range of possibly relevant confounding factors. Those it did adjust for (age, marital status, years of school, quality of housing) had an enormous effect on relative risk, changing estimates from 1.17 to 1.31 in men and from 0.66 to 1.24 in women, emphasising the fragility of the results.

The evidence relating passive smoking to lung cancer is more extensive than for IHD, being based on 27 published studies, not 13 as Kawachi et al state! While there is an association of spouse smoking to lung cancer risk that cannot plausibly be explained by publication bias, it cannot be reliably inferred this results from a causal effect of passive smoking. In the first place, exposure of nonsmokers to smoke constituents is very low. Thus typical nonsmokers retain only about 0.01-0.02% of the amount of smoking related particulates retained by a smoker (7). Furthermore, there are various sources of persistent bias in the epidemiology, a major one caused by misclassification of a

proportion of smokers as nonsmokers. As argued at length elsewhere (8-12) this bias can produce an artefactual association of a similar magnitude to the association claimed by Kawachi et al (1) to be due to passive smoking. Wells (2) correction for this bias was totally inadequate, failing to allow for the possibility of misclassified current typical regular smokers, whereas a recent summary of data from large studies shows an average rate of about 4% (11).

Although there is virtually no epidemiological data on risk in relation to workplace exposure to passive smoking, Kawachi et al (1) present estimates based on unjustified extrapolations from the spouse smoking estimates, which are themselves hopelessly biased.

The authors present numbers of deaths with ranges, so giving the uninformed reader a spurious idea of accuracy. When one considers no major authority has yet concluded passive smoking causes IHD; it is difficult to see what useful meaning one can attach to the cited lower limits of 39 IHD deaths for spousal smoking and 62 for workplace exposure.

Peter N Lee (Mr), PN Lee Statistics and Computing Ltd., Cedar Road, Sutton, Surrey SM2 5DA, UK.

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Failed vasectomy

A recent ACC appeal case was published in the Otago Daily Times and I found it very disturbing (see Medicolegal p 453). This couple was awarded compensation after the alleged failure of a vasectomy performed at Oamaru Hospital in 1979. After this operation it took nine months before the sperm count was zero. Nearly five years later the appellant's wife fell pregnant. These happenings can be easily explained in that the vasectomy was performed correctly but the sperm count took a long time to reach zero because the patient was slow to ejaculate all the sperm from his body. This is quite often seen. The pregnancy resulted from recanalisation of the vas deferens and can occur once in about every 500 vasectomies. Yet despite the above explanations, some other surgeon has stated that it is standard medical practice to recommend a repeat vasectomy after three or at the most four positive sperm tests after a vasectomy. Judge Middleton has accepted this surgeon's evidence as gospel and this persuaded the judge to allow the claim. If the facts of the case are as I read them in the Otago Daily Times then there has been a clear miscarriage of justice.

Compensation has been wrongly awarded and a doctor wrongly accused of negligence. This case may set a false precedent. The Accident Compensation Corporation should not be allowed to accept this appeal decision and this case should go to a higher court.

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Treatment of Frey's syndrome (gustatory sweating) with topical glycopyrrolate: case report

Treatment of Frey's syndrome with topical glycopyrrolate is well described in the specialist literature but is generally not well known. It is likely there are a number of people in New Zealand that have this problem, but who are unaware of this potentially effective and simple treatment. However when I saw my first patient with Frey's syndrome a few years ago, I soon discovered that topical glycopyrrolate was not something that was readily available.

Frey's syndrome or localised facial gustatory sweating and flushing is a rare condition which is most commonly seen as a sequelae of superficial parotidectomy. The patient, a 45 year old female, had had a left superficial parotidectomy five years before for recurrent parotitis. Following the operation, she developed sweating on the left side of her face whenever she ate and this caused significant social embarrassment. When the problem first occurred her surgeon had told her nothing could be done. In fact a number of treatments are available and include commercial antiperspirants, topical 20% aluminium chloride in alcohol, stellate ganglion blocks, tympanic neurectomy, and subdermal insertion of fascia lata grafts. I believe none of these treatments are as simple and generally as effective as topical glycopyrrolate.

Glycopyrrolate is a quaternary ammonium anticholinergic agent which does not cross the blood brain barrier, unlike scopolamine, and is associated with a very low incidence of side effects. It has been shown to be an effective treatment for Frey's syndrome (1,2). The glycopyrrolate (Bomack Laboratories) was formulated in two strengths, 1% and 2% and in two formulations, gel and a cream. The cream was prepared by dissolving the glycopyrrolate in a minimum amount of water and incorporating into cetomacrogol cream. The cream was adjusted to pH 3.0-3.5. The gel was prepared by incorporating the powder into Sonigel in which it rapidly dissolved.

The patient commenced treatment with 1% formulations and as these controlled symptoms for up to five days with the only adverse effect being an occasional dry throat, treatment was maintained at this strength. The gel was a cosmetically more acceptable formulation as the affected area extended into the hairline.

The main precaution is to avoid use in patients with narrow angle glaucoma.

The following instructions were supplied to the patient: (1) Avoid applying to nose, mouth and eyes. (2) Never apply to cut or infected skin. (3) Effectiveness may increase by applying twice in the same day, or by rubbing into the skin after application. (4) Always wash hands well afterwards with soap and water. Do not wash the treated part of the face for 3 to 4 hours. Avoid contact between the eyelids and the wash cloth used on the treatment area. (5) Keep well away from children. (6) Keep in a cool place. (7) If a significant side effect such as blurred vision or dry mouth occurs and persists, temporarily discontinue and contact your doctor. (8) Do not reapply until sweating occurs.

Thanks to Julie Knight, Intern Pharmacist, who developed the formulations.

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Passive smoking in New Zealand

Mr Lee's letter to the NZ Medical Journal (NZ Med J 1989; 102: 448) contains much the same arguments as in his previous efforts on behalf of the tobacco industry in New Zealand and other countries (1-4), each of which have previously been rebutted (5-7).

Mr Lee need not have pointed out to us that several studies of passive smoking and ischaemic heart disease involved small numbers of cases. Indeed he does not appear to have grasped that this is precisely the reason why we chose to use the results of a meta analysis in our estimates. What is important is the overall numbers in the meta analysis, not the numbers in selected subgroups in specific studies.

We fail to see the point that Mr Lee is trying to make in his comment about the Japanese prospective study; there is nothing

statistically implausible about a significant relationship between passive smoking and IHD failing to show up on 14 years' follow up (8), but appearing on 17 year follow up (9). Perhaps Mr Lee is unaware that the risk of IHD is related to duration of exposure (pack-years) to cigarette smoke, and that extending the duration of follow up increases the statistical power of the study?

We cannot specifically comment on Mr Lee's references to his own writings on misclassification bias. Two of his citations on this subject are references to papers given by Mr Lee himself at overseas conferences, which were therefore inaccessible to us. Nevertheless his claim that misclassification of a proportion of smokers as nonsmokers has led to an artefactual association of lung cancer with passive smoking appears most unlikely. It is just as likely that misclassification of passive smokers as nonexposed nonsmokers has led to an underestimate of the risks of passive smoking, ie, correcting this source of bias is likely to raise the relative risks of lung cancer and ischaemic heart disease.

Finally, we would like to acknowledge Mr Lee's comment that the evidence relating lung cancer to passive smoking is based on 27, not merely 13 studies. As Bradford Hill remarked (10), consistency of an observation across different studies increases our confidence in the belief that the association is causal.

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Is empathy unhealthy?

I have read with some amusement and interest the description of various occupational or hobby related syndromes, eg, space invaders' wrist, and triathlon tip, which surface in the medical literature from time to time. Each has described the hazards unwittingly encountered in one of a wide range of activities. Having been a recent sufferer from another such unexpected condition, and thus considerably less amused, I felt it appropriate to add to this mounting literature of cautionary tales.

Courses in interviewing skills stress the importance of nonverbal communication. It is not sufficient to use the right words, or right tone. The positioning of patient, doctor and desk affects the power balance between patient and doctor. We have been encouraged to move out from behind our desks, to sit close to the patient, and when appropriate to use touch in our communication. Body language including body posture must be congruent with the message we are attempting to communicate. A forward leaning body posture denotes a readiness to listen, a backward leaning (or, for most chairs, the sitting/straight up) position denotes a negative attitude (1).

The literature on this subject to my knowledge has concentrated on the effectiveness of the communication, and patient satisfaction. However, are there hazards that accompany this improved communication?

I report one case (myself) of cervical spine dysfunction leading to paresthesia in the brachial plexus distribution, in a patient with frequent thoracic facet problems in the past. The cause appears to be an occupational disease—that of "empathetic back"—too much body language of the "I am listening" variety. (An alternative label would be that of poor posture!)

Have other medical practitioners and those in other listening professions noted the same problem. Do we need to add to the literature yet another occupational disease?

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1. Peters P. Non verbal communication in the general practice surgery. In: Tanser BA. Language and communication in general practice. London: Hodder & Stoughton, 1978.

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Passive smoking in New Zealand

Mr Lee's letter [1] pretends to a scientific basis it does not have. Hirayama's first publication [2] focused on cancer of the lung among nonsmoking Japanese wives and set off a flurry of criticism of the methodology—including the analysis. The analyses have been redone showing significance enhanced by improved analysis. Only someone committed to nonsense would report a p-value for the difference between the two results.

Mr Lee's criticism of the study by Helsing et al [3] makes no sense on the face of it. Controlling for 'a whole range of possibly relevant confounding factors' has as much likelihood of heightening the significance as of lowering it. The researchers found that adjusting the relative risks has in fact enhanced the significance of their findings.

Mr Lee has a greater tolerance for assessing a study as 'published' than most scientists do, as demonstrated by his tenth reference. Perhaps he gives more weight to studies of 9 subjects which unsurprisingly fail to yield significant results than most epidemiologists would. He may not, however, show so little tolerance for the epidemiological methods he exploits. Spousal smoking has, again and again, been shown to be associated with lung cancer risk [4,5,6]. The biomedical underpinning—proven studies in animals and dose-related responses in humans—relating the constituents of both sidestream and mainstream tobacco smoke to production of cancers of the lung is undisputed [7,8].

Proximity of the non-smoker to the smoker over time rather than the concentration of single toxic substances in the ambient air determines the degree of exposure. Given the large numbers of exposed nonsmokers even a very low degree of risk has substantial impact.

Misclassification bias, a favourite theme of Mr Lee, is a two-edged criticism. As long as misreporting of exposure is as likely for cases as for controls misclassification depresses the relative risk. The risk will be overestimated only when cases whose husbands smoke deny their own actual smoking more readily than cases whose husbands do not smoke or when cases exaggerate their husbands' smoking more than controls do. Where actual exposure has been measured and compared with reported exposure the agreement has been high and the misreported exposure has not been in only one direction.

The validity of extrapolating exposure in the home to exposure at work raises other questions about indoor air. If the home setting is one where a nonsmoker can choose another room to be in than the one the smoker is in, then exposures at home would be lower than worksite exposures. In the workplace freedom to move away from the smoke source is generally denied. By extrapolating Kawachi et al [9] have probably underestimated the risk and the number of deaths attributable to passive smoking.

Common sense does more than pseudo-science can to produce credibility. The weight of the evidence is against Mr Lee and others whom the tobacco interests sponsor [10].

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Cancer registration working group

We regret that Dr Hitchcock (*NZ Med J* 1989; 102: 419) regards our letter on cancer registration [1] as incorrect. We can only repeat what actually occurred.

Dr Hitchcock mentions a submission from the Board of Health.

After two letters from the group seeking details the board finally stated:

'In reply to your letter of 22 October 1987 we believe there is nothing to be gained from pursuing the matters you raise in your letter. Our reference in our original letter referred to apparent breaches in the past and the need to provide effective controls.'

That is as much information on 'instances of breaches of confidentiality' as was ever received from the Board of Health despite the repeated requests from the group for information on actual instances. The board did not refer to any submission from private pathologists.

We repeat 'no individual, no doctor and no group provided the working group with information on breaches of confidentiality' [1]. The essential point is that, despite all our efforts, we could not find any substantiated evidence of an actual breach of confidentiality by the New Zealand Cancer Registry.

It should not be necessary, but it may be helpful, to emphasise that had the group been given information on any instance apparently involving a material breach of confidentiality we would have regarded this as a serious matter and sought to ensure a thorough, independent and sensitive investigation.

We would like to take this opportunity to thank the many organisations and individuals who submitted comments on our report to the Review Committee on Health Statistics. We appreciate the constructive criticisms and the general support for our proposals.

K R Cooke,	Department of Preventive and Social Medicine, University of Otago Medical School, Dunedin;
A J Gray,	Cancer Society of New Zealand, Wellington;
A F Burry,	Department of Pathology, Christchurch Hospital, Christchurch;
R Stewart,	Department of Surgery, Wellington School of Medicine, Wellington.

1. Cooke KR, Gray AJ, Burry AF, Stewart RJ. *NZ Med J* 1989; 102: 197.

Dietetic advice

I was interested to read the paper Children's diets: what do parents add and avoid? by Dr R P K Ford and colleague (*NZ Med J* 1989; 102: 443), with the analysis of advice on various food substances.

It is quite staggering to find that none of the 103 children interviewed for this article had been given dietetic advice. Over and over again we are concerned to find that general practitioners give detailed advice when they are not trained to do so. The whole question of diet and nutrition is underestimated and undervalued in the undergraduate and postgraduate curriculum.

Fortunately we have an efficient training programme for dietitians in New Zealand and, in my opinion, it is unethical and unprofessional to attempt to give patients detailed advice on diet when we have well trained and qualified colleagues available to undertake this task.

I was provoked to write such a letter because all too frequently we have people referred to hospital with complications of diabetes who have never had the opportunity to have a consultation with a dietitian, who could certainly have influenced their eating patterns.

D W Beaven,

Department of Medicine,
Christchurch Medical School,
Christchurch.

Informed consent

I recently received a copy of the New Zealand Medical Association's revamped informed consent/request for treatment form.

It is impossible for a patient to know that he/she has received an adequate explanation of risks etc when the patient is in no position to assess this. If any aspect of the operation is withheld or overlooked the patient has no way of knowing.

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presence, and found that nalidixic acid was contraindicated if there was history of convulsive disorders. I discontinued nalidixic acid and substituted cotrimoxazole.

I am happy to report the child has been free of convulsions for the last 5 weeks. Also there is a marked improvement in personality with no evidence of hyperactivity. I am unable to predict whether the child will be free of convulsions and hyperactivity in the future.

The lesson to be learnt from this experience is to listen to the concerns and observations of parents. They are with the child all the time. We cannot remember the side effects and contraindications of drugs all the time. If in doubt don't be reluctant to refer to the text book even in the presence of patients.

G A Paul,

Ngaruawahia.

The budget and certifying fitness for work

The policy of a single benefit for people temporarily excluded from the paid work force is good. Many factors hinder rehabilitation and it is unreal to pin it all on one. However the proposed greater monetary rewards for long term sickness disability will put more pressure on certifying doctors. I personally find assessment of sickness disability more difficult than accident. When one is paid by the patient, one must do the best thing for that patient, who often interprets this in purely financial terms. I find that patients, even ones I have never seen before, often resent any attempt to reassess disability. Patients will go to the doctor who takes the softest line. Clearly the budget proposals will not work unless careful consideration is given to the mechanism for determining who is fit for work.

People are excluded from the paid work force for eight reasons:
Lack of suitable employment. Very few people with long term disability are unable to do any sort of work. A caring society would reserve suitable jobs for the disabled. Certifying somebody fit for light work is futile as sporting enthusiasts prefer these jobs too. We are wedded to the concept of a forty hour working week. There would be many advantages if twenty hour week employment were more generally available. For many attempting rehabilitation this would be a much more realistic initial goal. I am dismayed at the budget target of 100 000 unemployed by the end of 1992. It would be fairer to aim at 200 000 working only twenty hours a week. Only the totally disabled should be excluded from the work force.

Lack of training and skills. These are required for most jobs suitable for people with disability. Retraining is the key to rehabilitation.

Care of other persons. Many are excluded from the paid work force by the needs of children and invalids. People often combine these responsibilities with paid employment but only if their health remains good.

Lack of motivation. I usually find that this is better described as having given up hope. What use is rehabilitation if there is no job? Where a patient has been on high wages the job that follows is likely to be lower paid. A major obstacle to rehabilitation would result from the proposed earnings related compensation for long term sickness disability.

Place of residence. People who have given up hope often attempt to make life bearable by moving to pleasant places. These are likely to be remote from rehabilitation facilities or employment opportunities. Others attempt to relieve boredom by becoming itinerant.

Congenital disabilities, illness, accident. These last three are the only causes that come into the area of expertise of the medical profession. Even here we often need the assistance of other disciplines. Seldom are medical conditions the sole causes of exclusion from the workforce. It is often impossible to say whether rehabilitation is possible unless rehabilitation has been tried.

I accept that certification by a doctor acting alone is the only practical way for short term disability. However I consider it unwise for these certificates to be renewable indefinitely, sometimes by a different doctor each time. I propose that a time limit of say six months be set. After that, assessment should be by a multidisciplinary team, whose chief function is rehabilitation. Patients should be reviewed annually. Even if the medical cause for exclusion from the workforce is unlikely to improve, the nonmedical causes may. I consider it wrong to tell clients that they are permanently useless.

Bruce Mackereth,

Mercury Bay Health Centre,
Whitianga.

Passive smoking in New Zealand

In replying to my earlier letter (NZ Med J 1989; 102: 448) Drs Kawachi and Pearce (NZ Med J 1989; 102: 479) misunderstand some important issues. They suggest I have not grasped the purpose of meta-analysis, because I pointed out many of the studies of passive smoking and heart disease are very small. Not so; I was making it clear the overall meta-analysis would be dominated by the two large studies, based on more deaths (1852) than the other five studies combined (226), and that there were major doubts about the findings from both of these large studies.

Drs Kawachi and Pearce seem to understand my criticisms of the Maryland study (1), but not my comment on the inconsistency of the two reports from Hirayama's study (2,3). Based on 14 years follow up and 406 heart disease deaths among female nonsmokers, Hirayama (2) reported relative risks, standardised for age and occupation, of 1.0, 0.97 and 1.03 according to whether the husband was (i) a nonsmoker, (ii) an exsmoker or a smoker of 1-19 cigarettes a day, or (iii) a smoker of 20+ cigarettes a day. Based on 17 years follow up and an extra 88 deaths, Hirayama (3) reported relative risks, standardised for age, of 1.10 and 1.30 for the same comparisons. If standardisation for occupation had no effect, it can be estimated that the relative risks for the last 3 years follow up would be 1.285 and 5.07; a magnitude of effect inconsistent with his previous results and also so large as to be totally implausible. If standardisation for occupation did have an effect, why did Hirayama not standardise for it in the later analysis?

The heart disease data, which contribute largely to the estimated number of deaths per year caused by passive smoking, are very unconvincing. The American Cancer Society million person study has provided the best evidence relating to spouse smoking and lung cancer (4) and it is unfortunate no similar data on heart disease have ever been presented. The study has far more deaths in nonsmokers than the Japanese or Maryland studies, and the quality of evidence is much superior.

Drs Kawachi and Pearce say they cannot specifically comment on my claim that misclassification of a proportion of smokers as nonsmokers might explain the observed association between passive smoking and lung cancer as two of my citations are to papers given at conferences. This overlooks all the other references, one to a book (5) available since 1986 which contains all the essential material. I have forwarded each of them a complimentary copy.

Drs Kawachi and Pearce quote the remark of Hill (6) that consistency of an observation across different studies increases confidence in the belief that the association is causal. This ignores the possibility of a common source of bias affecting all the studies. Misclassification of smoking habits is just such a bias. Measuring something 27 times with a faulty instrument is no better than measuring 13 times. What is needed is an accurate instrument. Until better studies are designed, estimates of deaths caused by passive smoking based on meta-analysis are likely to be seriously inaccurate.

The views I express do not necessarily reflect those of the tobacco industry. Many organisations consult me, including some tobacco companies, but the views I express are always my own, and the only reason for expressing them is to promote scientific understanding of issues of which I have expert knowledge.

Peter N Lee (Mr).

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Correspondence

Letters to the editor should be signed by all authors, typewritten in double spacing, and not exceed 800 words of text excluding references. References should be in the Vancouver style. Over-long letters may be shortened without reference to the authors unless it is specifically stated that they may not.

Passive smoking and passive thinking

Mr Lee's objection to the evidence on passive smoking (NZ Med J 1989; 102: 539) hinges on his theory that misclassification of a proportion of smokers as nonsmokers might explain the observed association between passive smoking and lung cancer. However his own book on the subject (1), which he cited, is itself a 100-page monument to bias. In it, he makes an exhaustive exploration of the possibility that smokers are misclassified as nonsmokers, while completely ignoring the fact that the smoking habits of the spouse are equally likely to be misclassified, thus biasing the relative risk estimate towards 1.0. Given the widespread exposure to passive smoking in society, it is likely that epidemiologic studies so far have underestimated the magnitude of risk.

Judging by his remarks on Hirayama's study (2), Mr Lee does not appear to have realised that the age and occupation-standardised rate ratios for ischaemic heart disease have been reported for 17 year follow up (2). The age and occupation-standardised figures were similar to the rate ratios standardised for age only (2). We have a complimentary copy of this paper available should Mr Lee wish to read it.

As with Mr Lee, the views we express are always our own. However, we do not receive any fees when we express them. Perhaps this helps clarify the issue of misclassification, which is really very straightforward, and almost invariably leads to an underestimation of the passive smoking effect.

Ichiro Kawachi,
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1 Lee PN. Misclassification of smoking habits and passive smoking: A review of the evidence. *International Archives of Occupational and Health Supplement*. Heidelberg: Springer Verlag, 1988.

2 Hirayama T. Lung cancer in Japan: effects of nutrition and passive smoking. In: *Musell M, Correa P, eds. Lung cancer: causes and prevention*. New York: Verlag Chemie International 1984: 175-95.

Treatment of hypertension

Kawachi and Purdie's reply (NZ Med J 1989; 102: 540) to my letter (1) raises important issues in the debate about the benefits of treating hypertension. Two main points require serious consideration. The first is contained in the advice that I should consult their data pertaining to treatment at a blood pressure greater than 100 mmHg (2), and to accept that these data represent the expected gain with treatment if hypertension is treated according to the recently published guidelines. This is wrong. The advice fails to recognise that the definition of hypertension by trial protocols is quite different from that suggested by recent guidelines, and it is not difficult to show that trial patients are unrepresentative of the larger population and are at lower risk even at equal levels of blood pressure because of exclusion criteria and the method of selection. A patient whose diastolic blood pressure is 100 mmHg after several readings taken over a reasonable time interval is at higher risk than if selected from a low risk population on the basis of screening measurements. In the placebo treated group of the MRC trial, whose records I am currently studying, the unadjusted cardiovascular event rate at entry for those with diastolic blood pressure greater than 100 mmHg ($n=3022$) was 8.1/1000/yr, but in those with the same blood pressure 3 months into the trial ($n=1198$) (equivalent to a definition of hypertension more in keeping with the guidelines) the corresponding figure was 10.3 (Millar and Lever, unpublished). This illustrates that current guidelines have the effect of identifying a subset of patients with a greater risk, thereby optimising the efficiency of treatment measured as the number of patients treated per event avoided, in this case 373 versus 116 respectively. These figures are much lower than those presented by Kawachi and Purdie (2).

The second point relates to the long term benefits of treatment. This is a complex and important issue which cannot be fully addressed here. Suffice to say that Kawachi and Purdie's suggestion that treatment can be deferred until the blood pressure

raises to unacceptable levels not only implies an arguable value judgment on their part but is illogical and not supported by any evidence that I know, though it has to be acknowledged as a possibility. No trial has shown that deferred treatment confers benefit (none has been designed to do so), and although left ventricular hypertrophy can regress with some forms of treatment (generally, the expensive ones!) there is evidence that permanent ultrastructural changes occur in the myocardium. Common sense suggests that treatment should be started as soon as a proper diagnosis according to current guidelines is made.

I noted the subtle change in the identity of the decision maker from the doctor to the patient in the case of my hypothetical 30 year old. This raises interesting questions. Whose is the responsibility if the patient makes the wrong decision? Is it realistic to expect him to review his decision at regular intervals, and if so, on what grounds will he reverse it? Will this happen before or after the onset of hemiplegia or dyspnoea?

The drug side effects are important for the patient and as a determinant of the overall ratio of costs to benefits. I believe the point I was making is clear enough and I leave it to practitioners to decide from their experience whether side effects such as impotence are reversible on withdrawal of the offending agent or not.

A previous paper from my correspondents' department has compared (unfavourably) the cost of treating hypertension with cardiac transplantation (3), and the clear implication from their publications is that they regard the treatment of mild hypertension as prohibitively expensive. We have agreed with their conclusion, up to a point (4,5) but have provided cost benefit analyses based on both trials of treatment and current management guidelines. It would be instructive to see similar calculations from Kawachi and Purdie.

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1. Millar JA. Treatment of hypertension. NZ Med J 1989; 102: 478.
2. Kawachi I, Purdie G. The benefits and risks of treating mild to moderate hypertension. NZ Med J 1989; 102: 571-9.
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Diet and behaviour

I write in response to the leading article, Diet and Behaviour (NZ Med J 1989; 102: 499). I am the mother of three children as well as being a general practitioner. Our 3½ year old daughter is food sensitive, and I have no doubt that the ingestion of foods or additives that disagree with her cause deteriorating behaviour, dark circles under her eyes, night waking (1.30 am-4.30 am), loss of appetite, increased thirst, vulvitis and joint pains. These reactions have been confirmed on several occasions by (often inadvertent) challenge tests. I have been manipulating her diet for a year with excellent results and improved sleep, and contest that, far from a negative effect, it has developed great responsibility and concern in her 5 year old sister that she should not be exposed to foods that make her ill.

Critical observation has long been the backbone of medical practice. Accurate deductions have been made before the process in question was understood. We need look no further than the development of vaccination by Edward Jenner, the correlation between handwashing and puerperal infection noted by Ignaz Semmelweis and the discovery of penicillin by Alexander Fleming.

Parents and teachers are the people best able to assess the behaviour of children. Early and subtle behaviour changes are unlikely to be noticed by independent researchers who do not know the children. We also are not aware of the cumulative effect of these small behavioural changes on the educational life of the

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Cardiovascular diseases and the work environment

A critical review of the epidemiologic literature on chemical factors

by Tage S Kristensen, MSc¹

KRISTENSEN TS. Cardiovascular diseases and the work environment: a critical review of the epidemiologic literature on chemical factors. *Scand J Work Environ Health* 1989;15:245-264. This is the second of two articles reviewing the epidemiologic research on cardiovascular diseases (CVD) and the work environment. It deals with chemical factors, ie. lead, cadmium, cobalt, arsenic, carbon monoxide, passive smoking, organic solvents, carbon disulfide, nitroglycerin, nitroglycol, and others. The epidemiologic literature relating to each is assessed on the basis of a number of methodological criteria, and the need for future research, the methodology of literature reviews, and preventive implications and perspectives are discussed. It is concluded that the causal relationship between two of the chemicals, carbon disulfide and nitroglycerin, nitroglycol, and CVD is very well documented. For lead and passive smoking a causal relation to CVD is likely. More research is needed concerning cobalt, arsenic, antimony, and other chemical compounds. Exposure to carbon monoxide increases the acute risk of CVD but has probably no lasting atherosclerotic effect. Cadmium and organic solvents are probably not causally related to CVD.

Key terms: antimony, arsenic, beryllium, cadmium, carbon disulfide, carbon monoxide, chemicals, cobalt, combustion products, dinitrotoluene, hypertension, ischemic heart disease, lead, nitroglycerin, nitroglycol, occupation, organic solvents, organophosphates, passive smoking.

This is the second of two articles on the work environment and cardiovascular diseases (CVD). It reviews the epidemiologic literature on occupational chemical factors and CVD. The results of the review are compared with those of earlier reviews in this field (1-13).

As in the previous article (14), I have dealt with occupational factors, but not with individual habits or characteristics. Thus, for example, I discuss passive but not active smoking, lead and cadmium but not soft water. To facilitate the best possible clarification of the occupational factors considered, I have also included investigations which are not strictly occupational because most of the exposures are also found outside the work environment.

The objectives of this article are the same as those of the previous one, ie. (i) to record and integrate the epidemiologic literature on CVD and the work environment; (ii) to evaluate the research with the objective of elucidating possible causalities between occupational factors and CVD; (iii) if possible, to point out areas where enough is known to start employing the research results for the purpose of prevention, and (iv) to point out defects and deficiencies in existing research with the objective of strengthening and improving future research efforts.

Materials and methods

The criteria for collecting and evaluating the epidemiologic literature have been described in detail in the previous article (14). The objective has been to include all epidemiologic studies on the exposures in English, German or the Scandinavian languages (or which have summaries in one of these languages). That objective has not been fully realized, although this review is more comprehensive than earlier reviews on the same topic. To give the readers an opportunity to supplement the review of the individual exposures, some special reviews from recent years have also been included. They contain extensive lists which also cover the nonepidemiologic literature.

The most important objective of the review has been to identify causal risk factors for CVD. With this in mind, I have evaluated the following five central methodological points for each study: (i) the time dimension, (ii) confounding, (iii) selection, (iv) measurement of exposure and disease, and (v) adequate design and statistical analysis. On the basis of this critical evaluation, each study has been given a score between "x" and "xxxxx" for methodological quality. (For more details of this scoring system, see reference 14.)

It should be emphasized that, when I refer to "study" in the following discussion, I do not necessarily mean an "article" or "paper." An article may contain two or more studies, eg. when the same hypothesis has been tested on two different populations, such as men and women or inhabitants of two different cities. If the analyses are published in such a way that the results for each individual group can be iden-

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Table 1. Results of 63 epidemiologic studies of cardiovascular diseases (CVD) and lead exposure according to the methodological quality of the studies. The table is based on references 28, 33—107.

Degree of relationship ¹	Methodological quality ²									
	I		II		III		IV		V—VI	
	N	%	N	%	N	%	N	%	N	%
+	—	0	—	5.3	—	0	—	0	1	1.6
+	—	0	—	0	—	0	—	0	—	0
0	8	44.4	6	31.6	6	25.0	—	0	20	31.7
+	5	27.8	2	10.5	2	8.3	—	0	9	14.3
+	3	16.7	9	47.4	18	66.7	2	100	30	47.6
?	2	11.1	1	5.3	—	0	—	0	3	4.8
Total	18	100	19	100	24	100	2	100	63	100

¹ + = negative relationship between lead exposure and CVD/blood pressure; 0 = slight or inconsistent negative relationship; 0 = no relationship; + = slight or inconsistent positive relationship; + = positive relationship; and ? = uncertain relationship.

² The criteria for methodological quality are explained in the text. No studies had scores for quality.

tified, they have been regarded as separate studies. On the other hand, the same research project is often published in several articles, eg, in prospective studies, in which successive results are published as the cohort grows older. In such cases, all articles have been evaluated as a whole with regard to study outcome and methodological quality.

Results

Lead

Many epidemiologic studies have been published on lead and CVD. Nonetheless, the topic is treated very superficially in the general reviews on the relationship between environmental exposures and CVD. In several more recent reviews, lead is not mentioned at all (3, 4, 7, 8), while the topic is treated very briefly with a maximum of three references in others (1, 2, 5, 9, 12). Only in the early review by Warshaw from 1960 (13), in Kurppa et al's review of 1984 (6), and in the reports of Rosenman (10, 11) is a reasonably thorough discussion of the possible lead-CVD relationship included. These authors give six to twelve empirical references. The general conclusion drawn by the authors who mention the topic is that further research is necessary.

In the more specific literature on lead, trace metals, or trace elements, similar divergencies are found. There are examples of CVD not being mentioned in reviews on lead and health (15) and of lead not being mentioned in reviews on trace metals and CVD (16—18). However, the most common conclusion in these reviews is again that further research is necessary (19—24). Some reviews do, however, conclude that lead has been shown to increase the risk of CVD, eg, Telesky's review from 1937 (25) and Stöfen's review from 1974, which primarily deals with German and East European studies (26).

In 1987 and 1988, two reviews were published which marked a new departure in this field of research. One is the comprehensive review by Sharp et al (27) on epidemiologic, clinical, and toxicologic studies con-

cerning low-level lead exposure and blood pressure. The other is a special issue of *Environmental Health Perspectives* (1988, volume 78), which contains papers and discussions from an international symposium on the relationships between lead and blood pressure. This issue contains several reviews of both experimental and observational investigations (28—32). The conclusion from these comprehensive reports is that it must be considered probable, though not yet definitively proved, that low-level lead exposure increases blood pressure and consequently the risk of CVD.

In the present review, 63 empirical studies have been evaluated (table 1). The empirical research in the field can be said to fall into three periods, ie, 1920—1962, 1963—1980, and 1980—the present. In the first period several studies were published on the topic, especially on the relationship between occupational lead exposure and blood pressure. The methodology of most of these studies is, naturally, rather primitive, but there are exceptions — for example, Vigdortchik's remarkable study from 1935 (51). I have included six of the investigations from this early period in my review. The second period, 1963—1980, was heralded by Dingwall-Fordyce & Lane's historical prospective mortality study from 1963 (64, 66). During this period, at least one investigation was published on the topic every year, but, as suggested earlier, these studies did not arouse any particular attention. From 1980 on, the situation has changed dramatically. Many more studies have been published (38 of the 63 investigations in table 1 are from the 1980s), and also interest is sharply rising in the possible relationship between lead and blood pressure at very low-level lead exposures, corresponding to those levels that the general population is exposed to from leaded gasoline, food, water, etc.

Table 1 reveals five features. First, many empirical investigations have been conducted. Second, virtually all the studies have a low or medium score for epidemiologic quality. Third, 30 investigations (48 %) show a clear positive relationship between lead exposure and CVD (or blood pressure), while nine (14 %) show a positive tendency. Fourth, a very clear relationship exists between study quality and study outcome. The percentage of positive studies increases as one moves from "x" to "xxxx" as follows: 17, 47, 67, and 100 %. Fifth, there is only one study which shows a negative relationship between lead exposure and CVD (33).

The large number of positive studies and the positive correlation between study quality and study outcome supports the hypothesis of a causal relationship between lead exposure and CVD.

A more-detailed examination of the 63 studies indicates that they are very different with regard to study design, study end points, and intensity of exposure. Many of the studies are, eg, cross-sectional investigations of the relationship between rather low levels of lead in blood and blood pressure, while others are historical prospective studies of mortality among

heavily exposed workers. However, further analysis shows that both the share of positive studies and the positive trend with increasing study quality are virtually the same when the different types of studies are analyzed separately.

While the relationship between low-level lead exposure and blood pressure, hypertension has been dealt with in detail in the earlier mentioned reviews from 1987 and 1988 (27—32), studies of lead workers with considerably higher levels of exposure have not. As these studies are of particular interest for occupational medicine, I have included six dealing with mortality in my review.

Dingwall-Fordyce & Lane (64, 66) found increasing cerebrovascular mortality with increasing lead exposure. The standardized mortality ratio (SMR) values were 94, 98, and 160 for employed lead workers as exposure increased and 76, 176, and 258 for retired lead workers, respectively. A later follow-up study showed the same trend, but — as expected — converging SMR values (65).

Cooper and his co-workers (57—59) found moderately elevated or normal SMR values for cerebrovascular mortality in two lead-exposed cohorts (SMR 132 and 93) but elevated values for "other hypertensive diseases" (SMR 475 and 320) and "hypertensive heart diseases" (SMR 203 and 128).

McMichael & Johnson (86) compared the mortality of workers with previous lead poisoning with the mortality of other lead workers and Australian men in general. Using proportionate mortality ratios, they found twice as many deaths due to cerebral hemorrhage and 24 % more deaths due to other cerebrovascular diseases among the formerly lead-poisoned workers than among the other lead workers. In a comparison with Australian men, the differences were even greater.

Davies (62) also studied men with previously registered lead poisoning and found an SMR of 410 for cerebrovascular diseases.

Selevan et al (93, 94) found fewer cerebrovascular deaths than expected (SMR 84), but even in this "negative" study the SMR values for cerebrovascular deaths increased with increasing exposure (< 5 years: SMR 47; 5—19 years: SMR 75; ≥ 20 years: SMR 146).

Finally, Gerhardtsson et al (40) found an SMR of 130 for cerebrovascular diseases among lead workers. Internal comparisons showed a positive correlation between both the mean blood-lead level and the peak blood-lead level and cerebrovascular mortality.

These six mortality studies of lead-exposed workers all have a medium level of epidemiologic quality. However, when the problems associated with historical prospective mortality studies are taken into consideration, the investigations show a rather consistent pattern with increased cerebrovascular or hypertensive mortality in the highly exposed groups. In addition, most of the studies showed an increased mortality as a result of chronic renal disease.

Even though studies with high methodological quality ("xxxx" or "xxxxx") are few, the following conclusions seem reasonable on the basis of the existing epidemiologic literature: (i) there is a causal relationship between lead exposure and blood pressure even at low exposure levels corresponding to blood-lead levels below 30 µg/dl (27, 28, 31, 70, 73, 74, 106); and, even if the relationship is weak, this relationship may have considerable public health implications due to the widespread lead exposure throughout the industrialized world (32, 72); (ii) there is an increased incidence of cerebrovascular diseases among workers who have been occupationally exposed to lead, but the clarification of the dose-response relationship is not possible on the basis of the existing studies; (iii) no studies have been found in which the incidence of ischemic heart disease (IHD) increased as a result of lead exposure.

Cadmium

The relationship between cadmium and CVD has been treated with considerable variability in general reviews on environmental exposures and CVD. A few authors dealt with the topic rather extensively (6, 10, 11, 13), but none gave more than 10 references. Others mentioned the possible relationship between cadmium and CVD but treated the topic very superficially (1, 2, 5), while the remaining authors did not mention cadmium at all (3, 4, 7—9, 12). In those articles in which the topic is discussed, it is concluded that the question is not sufficiently clarified and that further research is necessary.

In the special reviews on the associations between trace metals or cadmium and CVD, the possible relationship between cadmium and blood pressure is treated exhaustively by all the authors. In the older reviews from the 1960s and the first half of the 1970s, there is generally a belief in the hypothesis of a cadmium-blood pressure relationship (16—19, 108—110). Among these reviews, Schroeder's experiments on rats in the early 1960s play an important role. From 1976 on, skeptical articles and reviews (20, 23, 111—116) alternate with more positive ones (117—119). Considerable agreement exists regarding the relationship between cadmium exposure and increased blood pressure shown in animal experiments with rats, dogs, and rabbits, but there is no consensus on the interpretation of research on humans. After more than a quarter of a century of research comprising hundreds of experiments and investigations, Spieker et al (116) concluded in one of the most recent reviews: "The data available up to now [about the connection between human hypertension and cadmium pollution] can only be considered as a first step to clarify this problem [p 35]". This is, indeed, a modest profit from such great efforts.

In the present review, 33 investigations of cadmium and CVD (mainly blood pressure/hypertension) have been evaluated. In 11 of the studies, cadmium in blood,

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urine, hair, or kidneys has been compared for live hypertensive and normotensive persons. In nine studies persons who died from hypertensive heart disease or related causes have been compared with persons who died of other causes. In these studies, the cadmium content was generally measured from the kidneys or liver. Five studies are cross-sectional investigations of representative population groups for which the blood pressure has been related to cadmium in blood or urine. Four studies have related cadmium pollution in various city areas to morbidity and mortality, and the last four are occupational/medical studies. Table 2 contains a survey of the results and quality of these studies. The table indicates the following: (i) the studies examined have, in general, a low epidemiologic quality, and none of the studies have been rated "xxxx" or "xxxxx"; (ii) 13 of the studies (39 %) show (a tendency towards) a positive relationship [+ or (+)] between cadmium exposure and CVD; and (iii) there is a negative relationship between study quality and "positivity." Of the studies with a rating of "x," 46 % were positive; of the studies with a rating of "xx," 44 % were positive; and of the studies with a rating of "xxx," 27 % were positive.

Both the low share of positive studies and the negative trend in the table speak against the cadmium-CVD hypothesis. The conclusion therefore is that the null hypothesis is best supported by the investigations examined.

The methodological level of the research on cadmium and CVD (especially blood pressure/hypertension) is so low that an identification of the most common errors and flaws is important to facilitate their avoidance in future research. One of the worst problems concerns the measurement of cadmium exposure. Many studies estimated the exposure by measuring cadmium in blood (77, 80, 124, 137, 138, 140, 141, 148—151, 153). The blood cadmium level is, however, not a very reliable measure of the cadmium body burden. As early as 1976, Morgan (155) wrote: "Blood and urine may be convenient fluids to measure, but neither is well correlated with kidney or liver content, which together comprise about one half of the body burden (p 1361)." In contrast, the blood contains only

0.1 % of the body burden. Morgan recommended measuring cadmium in hair, kidneys, or liver. This view is strongly supported by other experts, including Lauwerys (112) and Perry & Kopp (119). Several studies have employed cadmium in urine as a measure of past exposure, but this measure must be regarded as being even poorer than cadmium in blood (77, 95, 107, 138, 144, 153). Seven of the 13 positive studies in table 2 have employed cadmium in blood or urine as the measure of exposure.

Two of the remaining six positive studies employed the cadmium content in air in a number of American cities as a measure of exposure. The results were then correlated to CVD mortality, and a positive relationship was found (131, 132). This method is problematic for many reasons. For example, the influence of cadmium in air on body burden is very slight. The significant factors are food, smoking, water, and occupational exposure.

Another major methodological problem concerns the study design employed. Many of the investigations employed a "quasi case-referent" design in which sick persons (with hypertension or IHD) were compared to healthy referents (77, 123, 124, 128, 130, 133, 140—142, 144—154). These studies are called "quasi case-referent" because in reality they are cross-sectional studies in which "disease" (hypertension, for example) is measured simultaneously with "exposure" (for example, cadmium in blood). This design is problematic for several reasons. First, because blood pressure and the blood/cadmium level are measured simultaneously, it is not possible to exclude the possibility that the direction of causation is reversed, i.e., that persons with hypertension have an increased content of cadmium in their blood due to metabolic changes. This possibility has, in fact, been mentioned by several authors, and one study directly concluded that hypertension increases the blood/cadmium level (141). Second, in most studies the selection of both cases and referents has been described very superficially or not at all. Since selection is of paramount importance in case-referent studies, this is an important potential flaw. Third, in many studies, the researchers had matched for smoking habits, and this is an error as tobacco smoking is not a risk factor for hypertension. In reality, it is overmatching because an important source of cadmium in the body is being blocked. Conversely, relative weight and education/social status have not been matched, and such matching should be done since both are risk factors for hypertension. Fourth, comparing normotensive and hypertensive persons leads to dichotomy. Instead, one should rather have operated with the whole spectrum of values on the blood pressure scale. This problem is especially important because many authors have hypothesized that the relationship between cadmium exposure and blood pressure has a reversed U shape with the largest effect at medium-high cadmium exposure levels.

Table 2. Results of 33 epidemiologic studies of cardiovascular diseases (CVD) and cadmium exposure according to the methodological quality of the studies. The table is based on references 55, 77, 80, 95—97, 107, 120—154.

Degree of relationship	Methodological quality							
	x		xx		xxx		x-xxx	
	N	%	N	%	N	%	N	%
-	—	0	1	11.1	—	0	1	3.0
(-)	—	0	1	11.1	3	27.3	4	12.1
0	3	23.1	3	33.3	5	45.5	11	33.3
(+)	2	15.4	—	0	3	27.3	5	15.2
+	4	30.8	4	44.4	—	0	8	24.2
?	4	30.8	—	0	—	0	4	12.1
Total	13	100	8	100	11	100	33	100

* See table 1 for an explanation of the symbols

Following this critique of methodology, and turning back to the empirical studies, I found only three positive studies which measured the cadmium content of the kidneys (128, 145, 147). These three studies are of the "quasi-case-referent" type just described and have so many methodological errors that they only scored "x" or "xxx" for methodological quality. Thus they can be considered to be of only very little significance.

Only three investigations have been found which are not "quasi case-referent" and which do not measure cadmium in blood, urine, or air, i.e. the historical prospective mortality study of 7000 workers by Kazantzis et al (120—122), the historical prospective mortality study of 525 workers by Andersson et al (134, 135), and the various projects concerning the Shipham inhabitants (125—127). These three studies scored "xxx" for methodological quality, and one of them — the Shipham study — showed a weak positive relationship between cadmium and CVD, while the two occupational studies showed a weak negative relationship.

Thus the conclusion seems clear, i.e. the epidemiologic research can in no way be considered to support the hypothesis of a causal relationship between cadmium exposure and hypertension or CVD in general. At this point it seems reasonable to conclude that such a relationship does not exist. Over the past 25 years, although the number of studies in this field has grown annually, the body of knowledge has not. Despite the last three studies mentioned, there is still a great need for epidemiologically sound studies on this topic.

Finally, tobacco smokers are moderately exposed to cadmium and should therefore have increased blood pressure. But the cardiovascular epidemiology shows very clearly that tobacco smoking is not a risk factor for hypertension. This lack of relationship, which has been epidemiologically very thoroughly investigated, is a further argument against the cadmium-blood pressure hypothesis.

Cobalt

In the mid-1960s, an epidemic of cardiomyopathies was registered in Belgium, Canada, and the United States among heavy beer drinkers. The cause of the epidemic was relatively quickly established. Several beer manufacturers had begun to add cobalt sulfate to the beer in order to stabilize the foam (156—161). Nearly half the patients examined in the various studies died from their cardiomyopathy. It is paradoxical that the consumption of 6—8 mg of cobalt sulfate per day could have this dramatic effect, as cobalt has been used in medicine in much higher doses without adverse effects. There seems to be agreement that the genesis of this unexpected adverse effect was a combination of cobalt exposure, long-standing high alcohol consumption, and poor nutritional condition.

In the general reviews on CVD and environmental exposures, the cobalt-related cardiomyopathies among

beer drinkers has been mentioned by several authors (2, 6, 9—11), while the remaining reviews do not mention cobalt as a risk factor for CVD at all. In addition, two case reports have been mentioned in a few of the reviews, i.e. those by Barborik & Dusek (162) and Kennedy et al (163). These case reports describe two cobalt-exposed men (41 and 48 years of age) who both died from cardiomyopathy. The authors suggested that cardiomyopathy caused by cobalt exposure might often be neglected and misdiagnosed.

In addition, three epidemiologic investigations of cobalt-exposed workers were found. In 1980 and 1983, Alexandersson & Atterhog (164, 165) published a study of workers in the hard metal industry who were occupationally exposed to cobalt (exposure level 0.01—0.06 mg/m³). The 146 exposed workers were compared to an unexposed reference group with regard to electrocardiography, pulse rate, and blood pressure. For the cobalt-exposed workers, Alexandersson & Atterhog (164) found a higher prevalence of hypertension, a higher average blood pressure, and more abnormal electrocardiographic changes. The electrocardiographic changes proved to a large extent to be reversible (165).

In an abstract from 1985, Horowitz et al (166) described cardiac manifestations of cobalt exposure in a group of 35 self-referred hard metal workers. Electrocardiographic abnormalities were found in 16 of the 35 workers.

The third study is a Danish investigation of female porcelain workers exposed to cobalt blue dye in their work (167). The median cobalt concentration in the air was 0.80 mg/m³. When the exposed women were compared with an unexposed reference group, no differences were found with regard to electrocardiographic changes or blood pressure, but a higher average pulse rate was found in the exposed group. The authors had no explanation for this finding.

Despite these empirical studies from the 1980s, a need still remains for more and better investigations of the relationship between occupational exposure to cobalt and heart diseases. In light of the widespread use of cobalt in industry and medicine (160), it is surprising that most of the literature deals with a brief epidemic of cardiomyopathy among beer drinkers.

Arsenic

In the general reviews on cardiovascular diseases and environmental exposures, arsenic and arsenic compounds are mentioned in seven (1, 2, 6, 9—11, 13) but not in six (3—5, 7, 8, 12). The seven reviews which deal with the topic include two to nine references to empirical studies. In Landrigan's special review on health effects from arsenic exposure (168), the cardiovascular effects were treated very briefly.

Three epidemiologic studies of arsenic exposure and CVD have been found. Pinto et al (169) investigated mortality among 527 retired workers from a copper smeltery during the period 1949—1973, while Lee-Feldstein (170, 171) studied a cohort of more than

8000 men during the period 1938–1977. Axelsson et al. (172) conducted a case-referent study in which the exposed persons were also copper smelters workers. In all three studies, the exposure was arsenic trioxide. In the two historical prospective studies, slightly elevated SMR values were found for CVD. Pinto et al. found a value of 109 for IHD and 113 for stroke, while Lee-Feldstein found SMR values of about 130 for IHD and about 120 for stroke. In both studies, a comparison was made with the mortality experience of the rest of the population in the area. In the study by Axelsson et al. which is the best of the three ("xxx" for methodological quality), an increasing relative risk for heart disease with increasing arsenic exposure was found (risk ratio 0.7, 3.0, and 5.6 for three exposure groups). The study by Pinto et al. scored "xx" for methodological quality, while the Lee-Feldstein study scored "xxx." Thus in these three investigations, clearer evidence for a relationship between arsenic exposure and CVD was found as the quality of the studies increased.

Furthermore, arsenic was part of the mixed exposure in Wingren & Axelsson's case-referent studies on mortality in the Swedish glassworks industry (52, 53). In these investigations a slight increase in CVD mortality was found.

In addition to these studies of exposed workers, there have been reports of a relationship between high levels of arsenic in drinking water and the development of both heart disease in children of northern Chile and peripheral vascular disease in adults from Taiwan (11). A special "arsenic beer scandal" took place in Manchester in 1900, when beer was accidentally contaminated with arsenic. More than 6000 persons became ill and 70 died, almost all from CVD (2, 156).

The relationship between another arsenic compound, arsine, and heart disease has been described by Pinto et al. (173). This study dealt with 13 poisoned men, of whom four died from acute myocardial infarction (AMI), while electrocardiographic changes were observed in the remainder. As far as is known, no epidemiologic studies have been conducted on the relationship between arsine exposure and CVD.

Even if the total epidemiologic research concerning the relationship between exposure to arsenic compounds and CVD is limited, a causal relationship is still likely. Further research is needed to clarify the relationship between the level and duration of the exposure and the risk for CVD.

Carbon monoxide

The relationship between carbon monoxide (CO) and CVD is dealt with in all the general reviews on CVD and environmental exposures (1–7, 9–13) except one (8). In a few of these reviews (1, 6, 10), the topic has been thoroughly treated, and many references have been discussed. Naturally, no disagreement exists on the potentially very serious consequences of acute high exposure to carbon monoxide, especially among per-

sons with existing atherosclerosis. But there is considerable uncertainty and conflicting views about the possible significance of carbon monoxide exposure in the development of atherosclerosis. A few reviews concluded, without any further documentation, that carbon monoxide increases the risk of IHD (7, 12). Others presented a more cautious point of view, which can be illustrated by way of the following three quotations: "(CO) may precipitate AMI or serious arrhythmias in persons with pre-existing coronary atherosclerosis" (p. 171) (5), "the question of whether CO is atherogenic remains unanswered even at the basic science level" (p. 1219) (3), and "there is surprisingly little evidence for a chronic atherosclerotic effect of CO" (p. 219) (11).

In addition to these general reviews, there are many special reviews on the negative health effects of carbon monoxide exposure (174–189). They contain detailed descriptions of the physiological mechanisms which result from the formation of carboxyhemoglobin in blood and present the results of many animal experiments. It will not discuss these topics in the present review; rather it should simply be stressed that the decrease in the oxygen-carrying capacity of the blood is greater than suggested by the percentage of carboxyhemoglobin because of the reduced release to the tissue of the oxygen carried by the remaining hemoglobin.

The specific reviews on carbon monoxide and health do not agree on the role of carbon monoxide in the etiology of CVD. The most "positive" reviews are probably the ones by Aronow (174, 175), Goldsmith & Aronow (177), and Atkins & Baker (176), while others are skeptical (179, 182, 188). In the remaining reviews no clear position is taken. Among the most skeptical reviews, Weir & Fabiano's critical reevaluation from 1982 (188) should be emphasized. The authors carry out an explicit and thorough discussion of the evidence for a causal relation between carbon monoxide and CVD. They specify the "three questions that best define the current areas of controversy: (i) Does chronic exposure to CO influence the development of atherosclerosis? (ii) By what mechanism does acute exposure to CO reduce maximal exercise ability in healthy persons and in persons with pre-existing CVD? (iii) Does acute CO exposure predispose individuals to cardiac arrhythmias? [p. 520]." In the evaluation of the empirical evidence for a causal relationship between carbon monoxide and CVD, it is important to keep these three questions separate, and I have attempted to do so in the following discussion.

For the present review, 22 empirical studies have been selected. Of them, most deal with persons who have been exposed to carbon monoxide occupationally, such as firemen, policemen, toll booth operators, garage personnel, motor vehicle examiners, bridge and tunnel officers, foundry workers, and blast furnace workers (190–210). (Reference 205 has been classified as two studies.)

Four of the empirical studies are not epidemiologic in the strict sense, but rather experimental (190–193).

In these four studies, which are very similar, 10 men with angina pectoris were exposed to different concentrations of carbon monoxide, and the duration of exercise before the onset of pain was registered. All four investigations found that the time before the onset of pain was significantly shorter after exposure to carbon monoxide even when the carboxyhemoglobin level was only about 1.5% higher in the exposed situation than in the control situation (193).

These results could have been expected because the angina patients already had IHD. Nevertheless, these experiments stress how dangerous an increased carboxyhemoglobin level can be for this group of patients. As the prevalence of IHD is high in the population, and as exposure to carbon monoxide is common — predominantly through smoking and exposure to the exhaust fumes from cars — this is a frequently occurring risk situation.

Two studies comparing the daily incidence of death from IHD with the level of carbon monoxide in the air can be said to elucidate the same complex of problems (195, 205). In one, the expected relationship was found between carbon monoxide levels and fatality from IHD, while the same relationship could not be shown in the other. Both studies had a low methodological quality.

While the aforementioned studies provide evidence of the influence of acute exposure to carbon monoxide on persons with ischemic heart disease, the remaining studies have tried to elucidate the role of carbon monoxide for the development of atherosclerosis. Table 3 contains a survey of these 16 studies. Table 3 illustrates the following two points: (i) most empirical studies on this topic have a low methodological quality ("x" or "xx"), and (ii) there is no relationship between study quality and study outcome, since half of the poor studies ("x" or "xx") and half of the better studies ("xxx" or "xxxx") have a positive study outcome (+ or (+)).

The best support for the hypothesis of a relation between chronic carbon monoxide exposure and the development of atherosclerosis comes from three positive studies with "xxx" or "xxxx" for quality (201, 208, 209). A closer examination shows, however, that not even these studies support the hypothesis very clearly. The cross-sectional study by Hernberg et al (201) on angina pectoris, electrocardiographic findings, and blood pressure among foundry workers found a relationship between carbon monoxide exposure and angina pectoris but not between carbon monoxide and electrocardiographic findings indicating IHD. Furthermore, slightly higher blood pressure was found among the persons exposed to carbon monoxide, but this finding could have possibly resulted from exposure to heat radiation. Altogether only the relationship between carbon monoxide and the prevalence of angina pectoris was convincing, and this relationship does not necessarily support the hypothesis of a lasting effect of carbon monoxide.

The older of the two studies by Stern et al (208) found an SMR of 105 for CVD among motor vehicle examiners. Closer analyses showed that the excess deaths occurred among examiners with zero to nine years of exposure (SMR for CVD 123). There was no increase in mortality among the examiners with longer exposure.

The more recent of the investigations by Stern et al (209), which concerned bridge and tunnel officers in New York City, is probably the best epidemiologic study of carbon monoxide and CVD ever published. The study showed significantly higher IHD mortality among the heavily exposed tunnel officers than among the bridge officers, who had a low level of exposure. However, there was no relationship to the duration of the exposure, and the excess mortality among the tunnel officers disappeared in the course of a few years after the cessation of exposure. This pattern closely resembles that seen in studies of tobacco smokers, in which the increased risk for IHD disappears relatively quickly after the cessation of exposure. This pattern does not fit the hypothesis of a lasting atherosclerotic effect of carbon monoxide exposure.

In light of the many studies on tobacco smoking and CVD, it is surprising that it is still not known why smoking increases the risk for CVD. A cross-sectional study by Wald et al (210) is often quoted to show that carbon monoxide increases the risk for atherosclerosis, but a later — and methodologically better — case-referent study by Kaufman et al (203) shows that the carbon monoxide content of cigarette smoke is unrelated to the risk of IHD among smokers.

All things considered, there is thus very little — if anything — in the empirical studies referred to which supports the carbon monoxide-atherosclerosis hypothesis. In the literature, the animal experiments by the Astrup-Kjeldsen group have played a large role, as these experiments apparently showed increased atherosclerosis in rabbits exposed to carbon monoxide. However, the group published a reevaluation in 1978. In these new investigations (211), they were not able to confirm the original findings, probably due to the fact that the original studies were carried out with small sample sizes and were not blinded. Several

Table 3. Results of 16 epidemiologic studies of cardiovascular diseases (CVD) and carbon monoxide exposure according to the methodological quality of the studies. The table is based on references 194–196–210.

Degree of relationship ^a	Methodological quality				Total
	x	xx	xxx	xxxx	
—	—	—	—	—	—
(—)	—	1	1	—	2
0	2	—	1	1	4
(+)	—	1	1	—	2
(+)	1	3	1	1	6
+	2	—	—	—	2
Total	5	5	4	2	16

^a See table 1 for an explanation of the symbols.

reviews, unfortunately, appear not to have been aware of this reevaluation.

Regarding the first of Weir & Fabiano's three questions, quoted on page 250, the following conclusions can be drawn: (i) there is no relationship between study quality and support for the hypothesis; (ii) very few studies are of high methodological quality, and these studies give almost no support for the hypothesis; and (iii) the research group behind the animal experiments, most often quoted in support of the hypothesis has withdrawn its results in view of established flaws in study design. Therefore, one can only concur with the conclusion of Weir & Fabiano "that there is no evidence to support the suggestion that exposure to low to moderate levels of CO increases the rate of the development of atherosclerotic disease in man. We believe that sufficient evidence is available to support the conclusion that, in fact, CO is not of pathogenic consequence in atherosclerotic disease [p 523]" (188).

Concerning the second of the three questions mentioned, Weir & Fabiano's conclusion also seems well-founded: "Acute exposure to low levels of CO does result in reversible, nonprogressive, exercise performance decrements in healthy and diseased individuals [p 523]" (188).

In the present review, I have not examined studies on carbon monoxide exposure and cardiac rhythm. Therefore, I refer the reader again to Weir & Fabiano, who concluded: "In summary, exposure to CO at acutely toxic levels results in alterations of cardiac rhythm, probably as a result of the induced hypoxia. There is no convincing evidence available to suggest that exposure to low to moderate levels of CO affects cardiac rhythm [p 523]" (188).

Even if these conclusions on carbon monoxide and CVD seem well-founded, there is still a need for further — and better — research in this field. In the epidemiologic area, there is specifically a need for the following: (i) prospective studies in which both the exposure and the development of the disease can be followed (none of the existing studies have been prospective), and (ii) studies in which carbon monoxide is not

an integrated part of a mixed exposure, which is the case with cigarette smoke, exhaust fumes, etc.

Passive smoking

Passive smoking has not been mentioned in any of the general reviews on CVD and environmental exposures, partly due to the fact that almost all research on passive smoking and chronic diseases — including lung cancer and CVD — has been conducted during the 1980s.

Most of the literature on passive smoking and CVD has, on the other hand, been reviewed in three thorough reviews on the health effects of passive smoking, i.e., the Surgeon General's report (212), the report from the National Research Council (231) — both from 1986 — and Fielding & Phenow's review from 1988 (214). These reviews all conclude that further research on CVD and passive smoking is needed.

The most important information concerning the studies which have been published currently on IHD and passive smoking is shown in table 4. These studies have all been published during the period 1983–1988 and are all based on a comparison of the incidence of IHD in nonsmokers married to smokers and nonsmokers married to nonsmokers. Five of the studies (215–220) are prospective cohort studies, while the last one (221) is a case-referent study.

As shown in table 4, the studies yielded nine estimates of relative risk. These estimates varied from 0.93 to 3.25 with an accumulation of values in the area of 1.24 to 1.31. The median relative risk for all the studies was about 1.3, and it is also approximately 1.3 when only the better studies ("xxx" or "xxxx" for quality) are considered separately. Only few of these relative risk values are significantly different from 1.0 when they are regarded individually. However, from this paper, more interested in the total pattern that appears when the studies are viewed as a whole.

A relative risk of 1.3 for passive smoking seems high in relation to the relative risk of about 2.0 often mentioned for active smoking. When comparing the two

Table 4. Review of the epidemiologic studies on ischemic heart disease (IHD) and passive smoking

Study	Study design	Population	Study quality ^a	RR for IHD ^b
Hirayama (215, 216)	16-year follow-up	91 450 women	xx	1.24
Gillis et al. (217)	6- to 11-year follow-up	827 men 1 917 women	xx	1.29 3.25
Gariand et al. (218)	10-year follow-up	695 women	xxxx	2.7
Svendsen et al. (219)	10-year follow-up	1 245 men	xxxx	1.61
Meising et al. (220)	12-year follow-up	4 162 men 14 873 women	xxx	1.31 1.24
Lee et al. (221)	Case-referent study of patients	41 male IHD patients and 133 referents 77 female IHD patients and 318 referents	xxx	1.24 0.93

^a The criteria for methodological quality are explained in the text

^b Relative risk for IHD among nonsmokers married to smokers compared to nonsmokers married to nonsmokers

values, one should keep in mind the following three facts: (i) the relative risk for active smokers is usually calculated with nonsmokers as the reference group, since nonsmokers are almost always passive smokers, and not really unexposed; too low a relative risk is yielded for active smoking; (ii) several studies indicate that the marginal effect per cigarette on the risk for IHD is highest at a low level of consumption and is thus not linear (222); and (iii) mainstream and side-stream smoke contain almost the same components, but not in the same proportions. One does not know why cigarette smoking increases the risk for IHD; therefore, it is difficult to extrapolate directly from active to passive smoking.

In evaluating today whether there is an increased risk for IHD among passive smokers, the biggest problem is not the statistical uncertainty or other methodological difficulties. In fact, the studies in table 4 are of rather high quality compared with the other research referred to in this article. The greatest problem must be assumed to be a possible publication bias, as it can, with some justification, be claimed that negative studies were of no interest until a number of positive studies were recently published. Therefore, more methodologically good studies of IHD and passive smoking need to be carried out and to be published regardless of the result.

In addition to the aforementioned studies of IHD and passive smoking, there are several investigations addressing the time lag before the onset of pain in angina pectoris patients exposed to passive smoking or carbon monoxide. These investigations have been referred to in the section on carbon monoxide since the increased level of carboxyhemoglobin is very probably the factor which provokes the earlier onset of angina. Finally, an abstract was published in 1987 by Moskowitz et al (223). It claims that passive smoking increases the risk of IHD among pubertal boys.

Even if more studies on passive smoking and IHD are still needed, it is now reasonable to conclude that the studies published have a high methodological quality, that the results are relatively consistent (relative risk for IHD about 1.3), and that a small, but increased risk for IHD is biologically plausible.

Organic solvents

A few of the general reviews treat organic solvents thoroughly (1, 2, 6, 10). Others treat the topic more superficially (3, 7, 9, 11, 13), and some do not mention it at all (4, 5, 8, 12). In those reviews in which the topic is dealt with, most of the emphasis is placed on the halogenated hydrocarbons (perchloroethylene, trichloroethane, trichloroethylene, fluorocarbons, methylene chloride, and other solvents containing chlorine, fluorine, bromine or iodine). Most of the studies mentioned have covered acute heavy exposures resulting in arrhythmia or sudden death.

Cardiovascular effects of exposure to organic solvents have also been treated in several special reviews

(224—227). Reinhardt et al (225) concluded that the sudden deaths in connection with acute heavy exposure to solvents were due to ventricular fibrillation due to sensitization of the heart to epinephrine. The review by Reinhardt et al also included a survey in which the solvents were evaluated according to cardiac sensitization properties. The most active group contained benzene, heptane, chloroform, and trichloroethylene. Steffey's review (226) of the cardiovascular effects of inhaling anesthetics is very thorough, listing 201 references. In addition, the review by Zakhari & Aviado (227) on the cardiovascular toxicology of halogenated hydrocarbons is both thorough and comprehensive (218 references and a very useful appendix with chemical formulas and properties).

The empirical basis for the aforementioned reviews consists primarily of animal experiments, which I have not discussed in this review, several case reports, and a few epidemiologic studies.

There are two types of case reports. They deal with exposure to very high levels of solvents either in connection with glue sniffing or in connection with occupational exposure. Glue sniffing has primarily been practiced by teenagers (224, 228—232), and many sudden deaths have been reported in both the United States and the United Kingdom, although a clear underreporting is likely since no anatomical changes can be observed in deceased persons. In some of the cases described, the strongly affected young "sniffer" stood up, started running, and then dropped dead (228).

The occupational case reports deal with workers who, in most instances, have been exposed to very high levels of solvents (231, 233—237). Most of the case reports concern the sudden death of healthy men 20—50 years of age after exposure to chlorinated solvents, but also after exposure to benzene (234) and methyl-cellulose paint (233). These case reports have many features in common, and several of the authors suggest that underreporting probably takes place with respect to this type of exposure also.

In addition to the case reports mentioned, five epidemiologic studies have been found (238—242). They were published during the period 1975—1988, and there is no indication of increasing research activity in this area despite the increased interest in organic solvents. The methodological quality score for these studies is medium ("xx" to "xxxx").

Speizer et al (238) studied the residents in a hospital pathology department who were exposed to fluorocarbon aerosols during the processing of cryostat sections and used radiology department employees as the reference group. They found a much higher prevalence of palpitation among the pathology residents and also a dose-response relationship between exposure to fluorocarbon 22 and the prevalence of palpitation. Moreover, resting electrocardiograms and 24-h electrocardiographic monitoring indicated premature atrial contractions, paroxysmal atrial fibrillation, and an in-

crease in premature ventricular beats. These results were unexpected in a group of young, healthy adults.

Kramer et al (239) examined 151 industrial workers who had been exposed to 1,1,1-trichloroethane and 151 matched referents. There was no difference with regard to electrocardiography, blood pressure, or serum cholesterol. Most of the persons examined were women, and most were below 35 years of age.

Blair et al (240) examined the distribution of causes of death among 330 deceased dry cleaning workers exposed to tetrachloroethylene. For CVD, a proportionate mortality ratio of 79 was found, significantly less than the "expected" value of 100. The proportionate mortality ratio has well known limitations, and this negative study only scored "xx" for study quality.

In the historical prospective study by Wilcosky & Tyroler (241), the mortality of 1284 workers exposed to several different solvents was analyzed. An excess frequency of deaths from IHD was found among workers who had been exposed to carbon disulfide, ethanol, and phenol.

Finally, Eskenazi et al (242) studied the prevalence of adverse pregnancy complications among 90 women exposed to organic solvents and 180 unexposed matched referents. They found a significantly higher proportion of women with preeclampsia (a disorder of pregnancy characterized by hypertension, edema, and proteinuria) and hypertension among the exposed women.

These epidemiologic studies are very different with regard to exposures, study design, and study end points. Therefore it is not possible to draw any conclusions on the basis of these investigations. No studies of occupational mortality have found increased CVD mortality among painters or other groups exposed to organic solvents. It is, therefore, not very likely that organic solvent exposure at moderate levels increases the risk for CVD.

Carbon disulfide

Carbon disulfide has been mentioned and recognized as a risk factor for IHD in virtually all reviews of CVD and environmental exposures published during the last 20 years. As will become apparent, this unique scientific consensus is primarily due to the Finnish study of viscose rayon workers, which was conducted by Hernberg, Nurminen, Tolonen, and their co-workers.

The first researchers to call attention to the relationship between carbon disulfide and IHD were Tiller et al, who in 1968 published their study of mortality among viscose rayon workers exposed to carbon disulfide (243). It actually consisted of two studies, one of the proportion of IHD deaths among workers from three factories, and the other a historical prospective mortality study of a cohort from one of the factories. Both studies showed a positive relationship between carbon disulfide exposure and IHD mortality.

The results from the study on Finnish viscose rayon workers have been published in many articles during

a 15-year period (244–253). Furthermore, the study has been used as a pedagogical example in one of the few textbooks on the epidemiology of occupational medicine (254). The study was a 15-year follow-up of two cohorts with 343 men in each. The study cohort was exposed to carbon disulfide in a viscose factory, but otherwise resembled the reference cohort, which worked at another factory in the same town. After about five years of follow-up, a relative risk of 5.6 for coronary deaths was determined for the exposed group. This finding resulted in several different interventions to reduce both the carbon disulfide level and the exposure of the individual workers in the viscose factory. Eight years after this intervention the relative risk was approximately one (248).

This exemplary epidemiologic study was scored "xxxxx" for quality. It is a prospective study over 15 years with good confounder control, reasonable knowledge of past and present exposure, many relevant study end points, a good, clear and understandable analysis, and intervention (reduced exposure) that was followed by the expected reduction in the disease studied. The study demonstrates that it is possible to convince the scientific community of a causal relationship via a "small" study of 2 x 343 persons if one has well selected study groups, a good analysis, and a lot of patience.

The relationship between carbon disulfide and IHD has been confirmed during the 1980s in American studies (255, 256), of which the latest (256) is the largest ever undertaken, the cohort studied comprising more than 10 000 workers.

Since the causal relationship between carbon disulfide and IHD is, with good reason, generally accepted, there is no reason to go into more detail. References to additional studies on this subject can be found in the very exhaustive reviews which have been published (257–261).

Nitroglycerin and ethylene glycol dinitrate (nitroglycol)

The relationship between heart disease and aliphatic nitrates is mentioned in virtually all reviews on CVD and environmental exposures, and it is one of the few relationships which all authors regard as definitively demonstrated. Nitroglycerin has been used both in the medical industry and for the production of dynamite since the middle of the last century. Ethylene glycol dinitrate has been used together with nitroglycerin for dynamite production since the 1930s, as ethylene glycol dinitrate improves the quality of the product and is cheaper. However, ethylene glycol dinitrate is far more toxic and more volatile than nitroglycerin.

The first studies of the relationship between nitroglycerin/ethylene glycol dinitrate and heart disease were published in Germany and Italy in the 1950s (262, 263). They were case descriptions of the phenomenon which has later been called "Monday morning angina".

na" or "Monday morning deaths." The nonfatal cases are attacks which resemble angina pectoris, but which are not provoked by exercise or psychic arousal. The attacks occur 1-3 days after exposure to nitroglycerin, ethylene glycol dinitrate ceases, and consequently the designation "nitrate withdrawal symptoms" has been used. This expression covers various conditions, such as anginal, coronary spasm, myocardial infarction, arrhythmia, and sudden death. In those instances in which autopsy was performed, normal coronary arteries were found.

Similar case reports have been published in other countries (264-266), and Morton's comprehensive review from 1977 (267) contains an excellent review of the literature concerning withdrawal hazards related to occupational habitation to aliphatic nitrates (74 references). It appears from Morton's review that, during the period 1952-1975, articles were published about Monday morning attacks in Germany, Italy, Japan, France, Sweden, Czechoslovakia, the Soviet Union, and the United States. It appears furthermore that the first American description was not Carmichael & Lieben's article from 1963 (264), as formerly believed, but an article from 1943 by Foulger (268). Foulger's article on "exposure to toxic chemicals" did not mention, however, that it concerned nitroglycerin/ethylene glycol dinitrate. [See, in addition, the correspondence between Foulger and Morton (269) and Morton's article on the ethical problems of concealing medical knowledge within occupational medicine (270)].

Half a year after Morton's review, Hogstedt & Avelson (271) introduced a new era in this research by publishing the first truly epidemiologic study. It was a case-referent study which was later supplemented with a prospective study (272) and with hygienic measurements (273), which together with two additional articles formed part of Hogstedt's thesis (274). In these works of high epidemiologic quality, it is documented in a convincing way that exposure to nitroglycerin/ethylene glycol dinitrate not only causes symptoms, diseases, and deaths due to nitrate withdrawal, but also raises the risk for CVD many years after the cessation of exposure.

Hogstedt's results have been confirmed during the 1980s by two other investigations (275, 276), both of which are historical prospective studies. In these studies, more CVD deaths were found than expected among the exposed workers despite preemployment screening and/or medical monitoring of the employees.

Thus it is now clear that nitroglycerin and, especially, ethylene glycol dinitrate increase the risk for CVD in the following two ways: partly via the specific "Monday morning attacks" due to nitrate withdrawal and partly via an increased risk for CVD which persists long after the cessation of exposure. This double effect is described in a few of the reviews, such as Fine's (1) and Kurppa et al's (6), while reviews on the topic were still being published during the 1980s which

only or almost exclusively describe nitrate withdrawal and "Monday morning attacks" (2, 3, 5, 277).

Other chemical substances and compounds

This section briefly reviews various studies concerning CVD and other chemical substances — areas in which only a few studies have been conducted or in which several "competing" exposures occur in the same study.

Dinitrotoluene. In 1986, Levine et al (278) published a historical prospective study of workers in two factories in which the employees had been exposed to dinitrotoluene (278). As in so many other instances, it was a suspicion of carcinogenicity which motivated the study, but no increased incidence of cancer was found among these workers. However, an increased incidence of IHD (SMR 141) appeared when the data from both factories were combined, with a relationship between the duration and the intensity of the exposure and the incidence of IHD. According to the authors, only very few of the workers had been exposed to nitroglycerin or ethylene glycol dinitrate.

Organophosphates. Two cross-sectional studies — one Danish (279) and one Indian (280) — have shown an increased prevalence of "ischemic" electrocardiographic changes among workers exposed to organophosphates. The Indian study included 155 exposed persons and 60 referents, while the Danish investigation included 446 workers, of whom 114 were classified as heavily exposed. In the Danish study, the higher prevalence of electrocardiographic changes among the heavily exposed individuals remained after control for age and smoking.

Antimony trisulfide. In the work by Briege et al from 1954 (281), a factory was mentioned in which 125 men were exposed to antimony trisulfide for eight months to two years. During this period, eight of the workers died suddenly. Two of the deaths were due to chronic heart disease. Four of the deceased were under 45 years of age. Because of this finding, the workers were examined, and electrocardiographic changes were found in 37 of the 75 examined. A review of the literature on animal experiments with antimony trisulfide seemed to show that the substance is cardiotoxic. At the factory studied, the use of antimony trisulfide was stopped, and no further sudden deaths were observed. In 12 of 56 reexamined workers, the observed electrocardiographic changes persisted. No other studies on antimony trisulfide were found in the literature.

Beryllium. In a historical prospective study by Wagoner et al (282), mortality was investigated in a cohort of 3055 workers who had been exposed to beryllium. Despite an assumed healthy worker effect, an SMR of 113 ($P < 0.05$) was found for heart disease in comparison with the mortality of American white

males. The highest value (SMR 129) was recorded for those exposed for at least five years.

Polycyclic aromatic compounds. In a case-referent study (283) of 6000 men employed by a primary aluminum smeltery, there were 306 new cases of IHD during the period 1975–1983. The persons concerned were compared with 575 matched referents. Among the blue-collar workers, a relative risk for IHD of 2.11 was found. The risk was particularly elevated among workers employed in the reduction divisions. These workers had a relative risk of 1.7 for IHD when compared with the remaining blue-collar workers. Unfortunately, the referents were matched for duration of employment, and this type of matching prevented the researchers from uncovering a possible relationship with the duration of the exposure.

Both a Danish (284) and a Swedish (285) mortality study of chimney sweeps found an excess frequency of IHD. The Danish study cohort consisted of 713 chimney sweeps, and the SMR for IHD was 222 when employed men were used as the reference. The Swedish study cohort consisted of more than 5000 chimney sweeps, and the SMR for IHD was found to be 135 when all Swedish men were used as the reference group. In both instances, the excess was significant at the 5% level.

In a historical prospective study of gas workers, Gustavsson & Reuterwall (286) found excess mortality due to IHD (SMR 125) and stroke (SMR 152). In this study, occupationally active persons in Stockholm were used as the reference group. Due to the small numbers, these results were not statistically significant.

Common for aluminum reduction workers, chimney sweeps, and gas workers is that they are exposed to combustion products. According to several authors (6, 284, 286), it can be hypothesized that polycyclic aromatic hydrocarbons or other polycyclic aromatic compounds are not only carcinogenic, but also increase the risk for IHD. This assumption is in accordance with the monoclonal hypothesis of atherosclerosis proposed by Benditt & Benditt (287), according to which atherosclerotic lesions might be derived from the proliferation of a single cell and could be considered to be benign tumors. The excess frequency of both IHD and lung cancer among Danish cooks and bakers (288) in the national Danish mortality study further supports this theory, as it must be assumed that many working in these trades are exposed to polycyclic aromatic hydrocarbons.

Concluding remarks

During my collection of the material for this review of the literature, I found no additional studies that could be judged as sufficiently relevant for inclusion. Since, of course, the judgment of which studies are

to be regarded as relevant is inevitably subjective, the reader may wish to supplement this review with other comprehensive ones dealing with CVD and chemical exposure (1, 2, 5, 6, 9, 10).

In a recently published article (283) concerning chemical exposures at work and the risk for IHD, the authors wrote: "Several personal risk factors are known to contribute to the development of IHD, but the effects of adverse working conditions have remained almost unexplored [p 659]" (283). This is a very widespread conception, but both the present review of the literature concerning chemical occupational factors and CVD and the previous article concerning non-chemical factors (14) have shown that the conception is not completely correct. Hundreds of studies, in fact, have been carried out in this field, and, in several areas, knowledge today is considerable.

The present review has, in some areas, confirmed other reviews of the literature, while in others the conclusions reached are contrary to the current view. For carbon disulfide and nitroglycerin/ethylene glycol dinitrate, the general opinion is confirmed. In these areas, studies have been conducted which have convinced virtually everybody about the causal relationship between these substances and CVD. It should be emphasized that what has convinced the scientific community is not the number of studies — as a matter of fact, there are very few — but the high methodological quality of the studies.

For lead and passive smoking, this review concludes more positively than others. The research concerning lead and CVD is very old, but not until recently has it been "discovered" in earnest. This phenomenon is, to a large extent, due to the remarkable results concerning low-level lead exposure and blood pressure from the National Health and Nutrition Examination Survey II, which were published in highly esteemed journals (70, 72). The research concerning passive smoking is new, and there are still relatively few studies, but they have a high quality and the results are consistent.

In other areas, the conclusions are more negative than usual, especially for cadmium and carbon monoxide. The research concerning cadmium and CVD is generally of poor quality, but the few good studies, together with the fact that tobacco smoking is not a risk factor for hypertension, makes it reasonable to conclude that cadmium is not a CVD risk factor. For carbon monoxide, the situation is more complicated, since there might be acute, short-term, and long-term effects. It is concluded that there are acute effects and possibly short-term, reversible effects, but that carbon monoxide does not increase the risk for atherosclerosis in occupationally exposed individuals.

In table 5, an attempt has been made to classify the possible cardiovascular risk factors which have been reviewed in this and the previous article. The basis for this classification is the view that empirical relationships are not "proved" once and for all. Hypotheses

are confirmed or invalidated through the collective and cumulative work which researchers carry out, and systematic critical reviews of the literature constitute an ever more important part of this process.

Several of the factors mentioned under "very definite" and "quite definite" in table 5 are widespread in industrialized countries. This is true for physical inactivity at work, noise, shift work, work strain, lead, and passive smoking. Even if the relative risk for CVD connected with each of these factors is modest (from approximately 1.1 to 2.0), the total etiologic fraction (attributable risk) will be considerable, and therefore the potential preventive benefit is great.

Now the classic question "Is enough known to use this knowledge for preventive activities?" arises. This is naturally not a scientific question but is still one with which researchers are often confronted and are expected to be able to answer. One answer could be that enough is known about the factors which have been mentioned under "very definite" and "quite definite" in table 5 to initiate prevention. There could however be a risk of making a mistake since one or more of the eight risk factors mentioned, at some point in the future, might prove not to be a risk factor for CVD. With respect to this possibility, the following two points are worth making: (i) if one chooses not to act until one has "100 % certain evidence," one is likely to make mistakes which have serious consequences for the health and mortality of many people, and (ii) the factors which have been mentioned in table 5 are all risk factors for diseases other than CVD. If one or more should prove not to be a risk factor for CVD, there would still be a positive effect from reducing or removing these factors.

It should be emphasized that table 5 only includes factors which have been mentioned in the literature as possible risk factors for CVD. The absence of evidence about a causal relationship should, of course, never be confused with evidence about an absent causal relationship. It should further be mentioned that the table deals with levels of exposure which occur "normally" at workplaces in Europe and North America.

Marmot & Theorell (289) recently claimed that psychosocial strain at work is probably part of the explanation for the negative correlation between social class and CVD incidence which is seen in industrialized countries. In their review, they emphasize Karasek's job strain model. The deliberations by Marmot & Theorell are an important supplement and corrective to the prevailing explanations which virtually always have their starting point in individual risk factors. It should be stressed, however, that not only job strain, but also several of the other factors mentioned in table 5, are more widespread in the lower social classes. Therefore changes in the work environment might contribute to the efforts to reduce the social inequities in morbidity and mortality which constitute an important target in the program "Health for All by the Year

2000" of the World Health Organization and in the health policy of many individual countries.

Finally, some remarks on the form and content of literature reviews within medical research. It is true for most reviews that the criteria for collecting the literature and for evaluating the individual studies are neither explicit nor systematic. The most common mode is that the authors of the review mention some positive and negative studies, observe the evident lack of consensus, and conclude that further research is necessary. This kind of review does not live up to elementary scientific demands and does not contribute to the development and clarification of research.

One of the consequences of the steeply rising number of scientific investigations all over the world is that researchers and other persons become ever more dependent on reliable reviews of the existing literature. Therefore reviews must try to live up to the demands for validity, reliability, precision, and reproducibility which are in force for the individual empirical studies. To the extent that reviews do live up to these scientific demands, they will be able to serve two very noble purposes: (i) the clarification of future research needs (one must not think only of stressing the ever present "need for more research," but of a sharper clarification of hypotheses, method and design problems, measurement problems, etc) and (ii) to indicate those areas in which the evidence is so "certain" that preventive activities ought not be postponed further. In this connection, it should be pointed out that some uncertainty must always be accepted, as is the case in other human and social contexts.

As is noted in this and the previous article (14), several reviews have been published in recent years in which attempts have been made to live up to the mentioned demands (5, 27, 188, 290—296). One must hope that development in the direction of more systematic reviews will continue in the years to come.

Table 5. Classification of possible risk factors for cardiovascular disease (CVD) in the work environment.

Causal relation to CVD	Risk factor	
	Nonchemical	Chemical
Very definite	Physical inactivity at work	Carbon disulfide, nitroglycerin/nitroglycol
Quite definite	Work strain (high demands and low influence), shift work, noise ^a	Lead, passive smoking
Possible		Cobalt, arsenic, combustion products
Somewhat possible	Heat, irradiation, power frequency magnetic fields, low frequency noise	Organophosphates, dinitrotoluene, antimony, beryllium, carbon monoxide ^b
Probably no relationship	Microwaves, cold ^c	Cadmium, organic solvents ^d

^a Increases the risk for CVD through increased blood pressure.

^b High-level exposure may be fatal, especially when combined with other risk factors.

^c High-level exposure may cause cardiac arrhythmias and sudden death.

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Passive Smoking and Heart Disease

Epidemiology, Physiology, and Biochemistry

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The first disease linked definitively to active smoking was lung cancer. It is, therefore, not surprising that the first disease identified as caused by passive smoking was also lung cancer.¹ Before the advent of mass-marketed cigarettes, lung cancer was a rare disease. Because smoking is the primary cause of lung cancer, identification of this link—for both active² and passive smoking³—was relatively straightforward. This situation contrasts with heart disease, which has many risk factors, and unsurprisingly, the scientific community was longer in concluding that active smoking caused heart disease.⁴ Once the link between smoking and heart disease was established, smoking was found to kill more people by causing or aggravating heart disease than lung cancer. In fact, smoking is the most important, preventable cause of coronary disease. Exposure to environmental tobacco smoke (ETS) has now been linked to heart disease in nonsmokers.^{5,6}

Much of the evidence for this link has appeared since 1986, when the US Surgeon General¹ and the National Academy of Sciences⁷ reviewed the evidence on the health effects of ETS. Based on the information available then, both reports concluded that the evidence linking ETS and heart disease was equivocal and that more research was necessary before any definitive statements could be made. These conclusions were reasonable in 1986. However, in the 4 years since publication of these reports, considerable information on both the epidemiology and biological mechanisms by which ETS causes heart disease has accumulated. Most of the results presented here were published after the 1986 Surgeon General and National Academy of Sciences reports.

There are now 10 epidemiological studies on the relation between exposure to environmental tobacco

smoke in the home and the risk of heart disease death in the nonsmoking spouse of a smoker and five epidemiological studies that examine nonfatal cardiac events. All but one of these studies yielded relative risks or odds ratios greater than 1.0. There are several lines of biological evidence that make this association plausible. There is evidence that exposure to ETS reduces exercise tolerance of healthy individuals and people with existing coronary artery disease. Such reduced exercise capability is one of the landmarks of acute compromises to the coronary circulation. There is good evidence, from both human and animal studies, that exposure to tobacco smoke, including passive smoking, increases aggregation of blood platelets. Such increases in platelet aggregation are an important step in the genesis of atherosclerosis. In addition, increasing platelet aggregation contributes to risk of coronary thrombosis, a cause of acute myocardial infarction. Last, carcinogenic agents in ETS, including benzo(a)pyrene, have been shown to injure the endothelial cells that line arteries. Such injuries are the first step in the development of atherosclerosis. Thus, exposure to ETS can contribute to short- and long-term insults to the coronary circulation and the heart. It is not surprising, therefore, that epidemiological studies have identified an increase in the risk of coronary artery disease in nonsmokers living with smokers.

Effects of Primary Smoking

Before reviewing the evidence linking ETS with coronary artery disease, summarizing the evidence that links active smoking with coronary artery disease is worthwhile. This evidence was summarized in the 1983 Surgeon General's Report,⁴ which was devoted entirely to cardiovascular disease; it concluded that cigarette smoking is one of the three major independent heart disease risk factors. It also concluded that the magnitude of the risk associated with cigarette smoking is similar to that associated with the other two major heart disease risk factors, hypertension and hypercholesterolemia; however, because cigarette smoking is present in a larger percentage of the US population than either hypertension or hypercholesterolemia, cigarette smoking ranks as the largest preventable cause of heart disease in the United States. Since 1983, an increasing body of evidence has shown that the polycyclic aromatic hydrocarbons

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TABLE 1. Epidemiological Studies of Environmental Tobacco Smoke and Coronary Heart Disease Death

Author	Type	Location	Deaths or cases (n)	Relative risk	95% Confidence interval	Dose* response?	Power† (%)	Controlling for
Males								
Gillis et al ⁸ (1984)	P	Scotland	32	1.3	0.7-2.6	-	5	Age
Lee et al ⁹ (1986)	C	United Kingdom	41	1.2	0.5-2.6	-	4	Age, marital status
Svensden et al ¹⁰ (1987)‡	P	United States	13	2.1	0.7-6.5	Yes	3	Age, blood pressure, serum cholesterol, weight, education, alcohol
Helsing et al ¹¹ (1988)	P	Maryland	370	1.3	1.1-1.6	No	40	Age, marital status, housing, education
Pooled§				1.3	1.1-1.6			
Females								
Hirayama ¹² (1984)	P	Japan	494	1.2	0.9-1.4	Yes	40	Age, diet
Gillis et al ⁸ (1984)	P	Scotland	21	3.6	0.9-13.8	-	2	Age
Garland et al ¹³ (1985)	P	California	19	2.7	0.9-13.6	-	2	Age, blood pressure, plasma cholesterol, weight, years of marriage
Lee et al ⁹ (1986)	C	United Kingdom	77	0.9	0.5-1.6	-	6	Age, marital status
Helsing et al ¹¹ (1988)	P	Maryland	988	1.2	1.1-1.4	Yes	2	Age, housing, marital status, education
He (1989) ¹⁴	C	China	34	1.5	1.3-1.8	Yes	3	Age, race, residence, occupation, hypertension, family history of hypertension or CHD, alcohol, exercise, hyperlipidemia
Humble et al ¹⁵ (1990)	P	Georgia	76	1.6	1.0-2.6	Yes	8	Age, serum cholesterol, blood pressure, weight
Butler ¹⁶ (1990)	P	California	64	1.4	0.5-3.8	-	4	Age
Pooled				1.3	1.2-1.4			
Both sexes combined								
Hole et al ¹⁷ (1989) ¶	P	Scotland	84	2.0	1.2-3.4	-	10	Age, sex, social class, blood pressure, cholesterol, weight
Pooled¶				1.3	1.2-1.4			

P, Prospective cohort; C, Case control; CHD, coronary heart disease.

*No entry in this column indicates no comment on the presence or absence of dose-response relation.

†Power to detect relative risk of 1.2 with 95% confidence.

‡High-risk population; members of Multiple Risk Factor Intervention Trial.

§Pooled relative risk computed as $R = \exp(\sum w_i \ln R_i / \sum w_i)$, where $w_i = (1/\ln R_i)^2$.¶ This report is a later follow-up of the population reported in Gillis et al.⁸¶ All studies combined without regard for sex, with Gillis et al⁸ excluded because Hole et al¹⁷ report later follow-up on the same people.

in cigarette smoke can injure the arterial endothelium and initiate the atherosclerotic process.

All the compounds from cigarette smoke that have been implicated as damaging to the cardiovascular system of active smokers have been identified in ETS.^{1,7}

Epidemiological Studies on ETS and Heart Disease

Since 1984, the epidemiological evidence linking exposure to ETS with heart disease has rapidly accumulated. The results of the 10 published studies⁸⁻¹⁷ that use death as an end point are summarized in Table 1 and Figure 1; four studies present data on men, eight on women, and one on both sexes combined. Despite minor differences in methodology or end points (some used death from ischemic heart

disease of any origin, and some were limited to death from myocardial infarction), the results of these studies are remarkably consistent. All the studies on men yielded relative risks of death from heart disease exceeding 1.0 when a nonsmoking man was married to a woman who smoked, with an overall risk of 1.3. All but one of the studies on women⁹ yielded relative risks exceeding 1, with an overall relative risk of 1.3. Five studies^{10,17-19,20} have also suggested an increase in the risk of nonfatal coronary symptoms, including angina and myocardial infarction. Consistency of an observation across different studies increases the confidence that a particular association is causal.

Several investigative teams also observed a dose-response relation between increasing amounts of

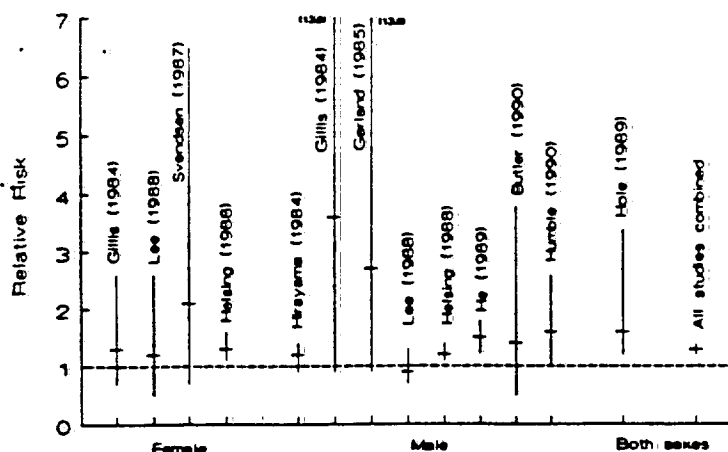


FIGURE 1. Graph of relative risk in epidemiological studies of the risk of death from coronary heart disease or myocardial infarction among nonsmokers living with smokers compared with nonsmokers living with nonsmokers. Lines indicate 95% confidence intervals. Note that two studies have upper bounds to the 95% confidence interval off the scale of the graph.

smoking by the spouse and the risk of heart disease in the nonsmoking spouse,^{11-15,17} which in most cases was statistically significant. The presence of such dose-response effects across multiple studies, conducted in different locations with different criteria, supports the hypothesis that ETS causes heart disease in nonsmokers.

While all but one of the studies in Table 1 and Figure 1 yielded relative risks greater than 1.0, the fact remains that three of the studies in men and five of the studies in women had 95% confidence intervals for the relative risk of passive smoking for heart disease that included 1.0, meaning that the risk was not statistically significantly elevated above 1.0 (with $p < 0.05$). Of note, the 95% confidence intervals do not lie symmetrically about 1.0 but are skewed toward higher risks. By examining the confidence intervals, the conclusion is reached that exposure to ETS elevates the risk of heart disease (Figure 1). Also, the results of these studies may be combined in a formal analysis to derive a global estimate of the relative risk and associated 95% confidence interval. By combining the studies, the sample size and, therefore, the power to detect an effect increases. Wells⁵ used then-available studies^{8,9,11-13,18} to compute a pooled relative risk of 1.3 (95% confidence interval, 1.1-1.6) for men and 1.2 (95% confidence interval, 1.2-1.4) for women. Our analysis on all the studies in Table 1 yields a combined relative risk of 1.3 (95% confidence interval, 1.2-1.4).

When interpreting the results of such epidemiological studies, it is always important to consider biological plausibility and potential confounding variables that can explain the results. Aside from noting that the hydrocarbons in mainstream smoke already implicated in heart disease are also in ETS, we will defer the discussion of biological plausibility until we discuss the effects of ETS on platelets and the atherogenic agents in ETS. For now, we will concentrate on potential confounding variables, which are particularly important in a disease like heart disease

because it is known to be caused by multiple risk factors.

All the studies controlled for the most important confounding variable, age, and several^{10,13-15,17} controlled for known risk factors for coronary artery disease, in particular levels of serum or plasma cholesterol, blood pressure, and body mass. Most of the studies also included one or more measures of socioeconomic status, such as housing or education. Indeed, studies that estimated the relative risk both with and without taking these confounding variables into account found an increase in risk associated with ETS after taking the confounding variables into account.^{10,15}

Lee²¹⁻²³ suggested that the elevated risk of heart (and other) disease with passive smoking may be due to misclassification of nonsmokers who are really smokers. In addition, Wald²⁴ noted that some people who say they live with nonsmokers have detectable levels of the nicotine metabolite cotinine in their blood, indicating that they are actually exposed to ETS, either at work or at home. The former type of misclassification tends to lead to overestimating the risks associated with ETS and the latter leads to underestimating the risk. Careful analysis of the question of misclassification, which applies generally to studies of ETS, has demonstrated that the observed risk cannot be explained by this problem.^{5,24-28}

The possibility always exists that some other confounding variable relates to cultural factors, such as the nature of housing or employment or the nature of time spent outside the home. Also, it is possible that there are other confounders, such as a correlation of spouses' poor health behaviors (e.g., diet), which are not controlled for in analysis. The fact that results are from all over the world in widely varying cultural settings—including several regions in the United States, the United Kingdom, Japan, and China—argues against this concern.

One can assess formally the confidence in reaching a negative conclusion by computing the power of the study to detect an effect of specified size.²⁹ Table 1

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shows estimates of the power of each of the studies to detect a 20% increase in risk of heart disease (i.e., a relative risk of 1.2) with the available samples. The power was computed as described in Muhm and Olshan,³¹ using a two-sided test for the relative risk with a type I risk of 5% (i.e., requiring the 95% confidence interval for the relative risk to exclude 1.0 before concluding a statistically significant elevation in risk in an individual study). Most of the studies have low power. This low power of the individual studies argues against drawing an overall negative conclusion concerning the link between ETS exposure and risk of death from heart disease, based on the individual studies taken one at a time.

Last, and of note, all these studies are based on the smoking habits of the nonsmoker's spouse and, therefore, the exposure to ETS at home. Household exposures to ETS at home are generally much smaller than exposures at work, where the density of smokers is generally higher.^{31,32} As a result, these studies generally underestimate the risk and attendant public health burden due to ETS-induced heart disease. Kawachi et al³³ adjusted Wells's⁵ relative risks to account for workplace exposures to ETS and found that the relative risks increase to 2.3 (95% CI, 1.4–3.4) for men and 1.9 (95% CI, 1.4–2.5) for women. Thus, any potential confounding of the results because of exposure to ETS outside the home will tend to produce underestimates rather than overestimates of the effect of ETS. Likewise, estimates of public health impact based on risks computed from household exposures⁵ will be lower than the true public health impact. In addition, Wells⁵ and Kawachi et al³³ indicate that the number of heart disease deaths due to passive smoking is an order of magnitude greater than the number of lung cancer deaths due to passive smoking. Even though the relative risks for heart disease and lung cancer caused by ETS are similar (about 1.3 for both diseases), the attributable deaths for heart disease is greater because heart disease is much more common than lung cancer. Of 53,000 annual deaths in the United States attributed to passive smoking,⁵ 37,000 are attributed to heart disease compared with 3,700 for lung cancer (Figure 2).

These epidemiological studies demonstrate a connection between ETS exposure and death from heart disease. We now turn our attention to possible physiological and biochemical mechanisms that explain these observations.

Short-term Effects of ETS Exposure

Long-term exposure to ETS exerts carcinogenic effects by increasing the cumulative risk that a carcinogenic molecule from ETS will damage a cell and then initiate or promote the carcinogenic process. The situation with heart disease is different. In heart disease, important long-term changes (i.e., the development of atherosclerotic lesions) and short-term changes occur. The latter include an increased myo-

Deaths from Passive Smoking Total Deaths: 53,000

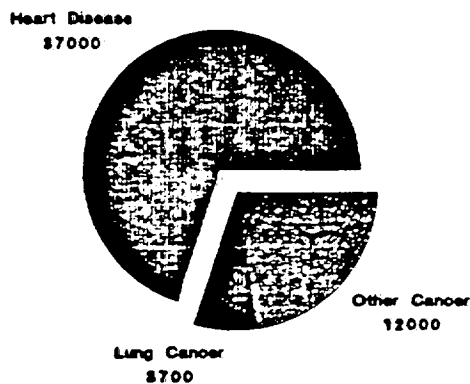


FIGURE 2. Pie chart of US deaths from environmental tobacco smoke. The majority of annual deaths are attributed to heart disease. Modified from Wells.²⁶

cardial oxygen demand that may outstrip the oxygen supply and produce ischemia and an increased platelet aggregation that may lead to coronary thrombosis and acute myocardial infarction.

When the coronary circulation cannot provide enough oxygen to the myocardium to meet the demand, the result is ischemia, which can be a silent or an anginal episode. Earlier onset of angina or hypotension during exercise is a reflection of more severe heart disease. Oxygen supply can be reduced by atherosclerotic narrowing or vasoconstriction of the coronary arteries or by reducing the oxygen-carrying capacity of the blood because the carbon monoxide in the ETS forms carboxyhemoglobin, which, in turn, reduces the blood's oxygen-carrying capacity. Khalifen and Klockkov³⁴ confirmed earlier work by Aronow³⁵ demonstrating that exposure to ETS significantly reduced both the exercise ability in patients with coronary artery disease and the rate-pressure product (heart rate multiplied by systolic blood pressure). In both studies, patients were exposed to realistic levels of ETS by sitting in a waiting room while someone was smoking. These effects were present in smokers and nonsmokers³⁴ and regardless of whether the room was ventilated.^{34,35} Exposure to ETS also increased resting heart rate and systolic and diastolic blood pressure and resulted in a lower heart rate at the onset of angina.³⁵ Blood carboxyhemoglobin was increased by about 1% after exposure to ETS.³⁵ Thus, short-term exposure to ETS leads to an imbalance between myocardial oxygen supply and demand during exercise in patients with coronary artery disease. While this discussion has concentrated on the carbon monoxide in ETS as the active agent, some other component of the ETS may be causing or contributing to this effect.

The effects of ETS on cardiac performance are, in fact, severe enough to affect exercise performance in

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young healthy subjects with no evidence of heart disease. McMurray et al³⁶ exposed young healthy women to pure air and air contaminated with ETS while they exercised on a treadmill. The results were similar to those observed in patients with coronary artery disease. Resting heart rate was increased during exposure to ETS, which increased blood carboxyhemoglobin by about 1%. Exposure to ETS significantly reduced maximum oxygen uptake (by 0.25 l/min) and time to exhaustion (by 2.1 minutes). Exposure to ETS also increased the perceived level of exertion during exercise, maximum heart rate, and carbon dioxide output. It also significantly increased levels of lactate in venous blood (from a mean of 5.5 mM during the control period to 6.8 mM after exposure to ETS). This greater lactate at a lower oxygen consumption during the passive smoking trials indicates a greater reliance on anaerobic metabolism. The combined effects of the reduced oxygen-carrying capacity and increased lactate resulted in a reduction in maximal aerobic power and the duration of exercise. Thus, even in healthy subjects, exposure to ETS adversely affects exercise performance. Lamb³⁷ suggested that at maximal exertion levels, up to 90% of the oxygen-carrying capacity of the blood may be needed. Probably because of carbon monoxide, ETS reduces this capacity, so the muscle cannot maintain its high rate of aerobic metabolism unless cardiac output is further increased; people with heart disease and reduced ventricular reserve have difficulty meeting this demand. In sum, exposure to ETS increases the demands on the heart during exercise and reduces the capacity of the heart to respond. This imbalance increases the ischemic stress of exercise in patients with existing coronary artery disease and can quickly precipitate symptoms.

Moskowitz et al³⁸ found evidence that adolescent children of parents who smoked may suffer from chronic tissue hypoxia such as that observed in anemia, chronic pulmonary disease, cyanotic heart disease, or high altitude. These children had significantly elevated levels of 2,3-diphosphoglycerate (DPG), even after correcting for age, weight, height, and sex. DPG acts as a physiological modulator of hemoglobin oxygen affinity. It binds to specific amino acid sites and increases the P_{50} (lowers the oxygen affinity), thus making more oxygen available to peripheral tissues. This observation suggests that the body is attempting to compensate for hypoxia by increasing the DPG level in blood to meet tissue oxygen requirements. The changes were dose dependent; the greater the exposure to ETS (measured both in terms of parental smoking and serum thiocyanate levels in the children), the greater the increase in DPG.

There is also evidence that short-term exposure to ETS directly affects respiration of the myocardium at a cellular level. Gvozdková et al³⁹ exposed rabbits in a 50 l child's incubator to the smoke of three burning cigarettes smoked during a 30-minute period, and they measured several variables related to

the metabolism of cardiac mitochondria. They had three groups of rabbits: one group was exposed to a single dose of ETS, one group was exposed to 30 minutes of ETS twice daily for 2 weeks, and one group was exposed to 30 minutes of ETS twice daily for 8 weeks. They measured mitochondrial respiration as the consumption of oxygen after adding ADP to a vessel containing mitochondrial fragments. Using pyruvate as a substrate, mitochondrial respiration was reduced significantly compared with control (pure air) for all doses of ETS, by even a single exposure, to about half the control value. The oxidative phosphorylation rate was also reduced significantly at all exposures by about one third. There were no significant changes in the coefficient of oxidative phosphorylation with ETS exposure. Gvozdková et al³⁹ concluded that pyruvate as a substrate was a sensitive indicator of the toxic action of the ETS on the oxidative process.

Later, to further isolate where in the process of mitochondrial respiration the ETS acted, Gvozdková et al⁴⁰ and Gvozdkák et al⁴¹ reported data on succinate, NADH, and cytochrome oxidase activity in the mitochondria in the four groups of rabbits. Exposure to ETS affects the activity of NADH oxidase, succinate oxidase, and cytochrome oxidase of myocardial mitochondria. The activity of the first two oxidases exhibited no changes compared with the control group, neither after a single exposure to ETS or after exposures to 2 weeks. Cytochrome oxidase activity decreased both after a single exposure to ETS and over time, with greater decreases as the duration of exposure to ETS was extended. The observation that cytochrome oxidase and not NADH or succinate oxidase activity was affected by ETS suggests that the deleterious effects of ETS on myocardial mitochondrial respiration occur at the terminal segment of the mitochondrial respiration process. Prolonged exposure to carbon monoxide has been shown to induce ultrastructural changes in myocardium⁴²⁻⁴⁴ and may account for the adverse effects of ETS exposure on mitochondrial function.

Thus, short-term exposure to ETS not only increases the demand and compromises the supply of oxygen to the heart, but also reduces the myocardium's ability to use the oxygen to create ATP to provide energy to support the heart's pumping activity.

Effects on Platelets

The action of ETS to increase platelet aggregation is another way in which ETS can increase the risk of a coronary event. Platelets are important for the normal process of hemostasis, to prevent blood loss after an injury. When blood platelets aggregate inappropriately and form a thrombus in the coronary circulation, they can precipitate a myocardial infarction. Hemostasis depends on complex interactions among the dynamics of blood flow, components of the vessel wall, platelets, and plasma proteins. Definitive evidence has confirmed that platelets play a major role in thrombus formation and embolization.

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TABLE 2. Effect of Passive and Active Smoking on Platelet Aggregation and Endothelial Cell Damage

	Platelet aggregate ratio			Endothelial cell count			n
	Before	After	Change	Before	After	Change	
Passive smoking (nonsmoker) ¹	0.87	0.78	-0.09	2.8	3.7	0.9	10
Tobacco (nonsmoker)	0.80	0.65	-0.15	2.3	4.8	2.5	20
Nontobacco cigarette (nonsmoker)	0.81	0.78	-0.03	2.5	3.0	0.5	
Inhale cigarette (smoker)	0.81	0.68	-0.13	4.0	5.4	1.4	24
Not inhale cigarette (nonsmoker) ¹	0.82	0.73	-0.09	3.3	4.7	1.4	22
Smoke (smoker)	0.85	0.70	-0.15	4.4	6.4	2.0	17
Snuff (smoker)	0.82	0.76	-0.06	3.9	4.7	0.8	

All studies are paired and reflect significant differences ($p < 0.005$). Platelet aggregate ratio is the ratio of platelet count of platelet-rich plasma, prepared immediately after venipuncture with a solution containing edetic acid and formaldehyde, to that of platelet-rich plasma prepared in the same manner, except for the absence of formaldehyde. A decrease in the platelet aggregate ratio reflects an increased formation of platelet aggregates. Endothelial cell count is mean number of anuclear cell carcasses in 0.9- μ L chambers. Modified from Davis et al.^{47,48,51,52}

especially in the arterial system. In addition, increasing evidence has shown that platelet deposition and thrombus formation can contribute to the growth and progression of atherosclerotic plaques.^{45,46} An arterial thrombus appears to develop in three phases: platelet adhesion, platelet aggregation, and activating of clotting mechanisms. Passive smoking increases platelet aggregation and, thus, increases the likelihood of thrombus formation and myocardial infarction.

Table 2 summarizes the results of several studies by Davis et al.⁴⁷⁻⁵⁰ on the effects of cigarette smoke on platelet aggregation and damage to the arterial endothelium. Davis et al.⁵¹ also measured platelet aggregate ratios and endothelial cell counts in nonsmokers before and after exposure to 20 minutes of ETS while sitting in a hospital atrium. The platelet aggregate ratio in these studies is the ratio of the platelet count of platelet-rich plasma prepared from blood mixed immediately with EDTA and formaldehyde to the same mixture without formaldehyde. This method assumes that platelet aggregates circulating in blood are fixed in the EDTA-formaldehyde solution and that they break apart in the EDTA solution. Thus, a decrease in the platelet aggregate ratio reflects an increased formation of platelet aggregates. Mean values before and after passive smoking were 0.87 and 0.78 ($p = 0.002$) for platelet aggregate ratios and 2.8 and 3.7 ($p = 0.002$) for counts of anuclear endothelial cell carcasses in venous blood. These changes are intermediate between the effects observed after nonsmokers smoked two tobacco cigarettes and the effects observed after smoking two nontobacco cigarettes⁴⁷ and similar to the values observed in nonsmokers who smoked two cigarettes while trying not to inhale.⁴⁸ These effects were not correlated with the level of nicotine in the blood of the experimental subjects in any of these or other^{49,50} related studies on how drugs modify platelet aggregation and endothelial cell counts. In particular, the effects observed in nonsmokers who smoked without inhaling were similar to the effects on smokers who smoked two cigarettes even though the plasma nico-

tine levels in the nonsmokers were five times lower than those observed in the smokers.⁵⁰ Other work in the same laboratory comparing smoking with snuff use revealed similar changes in platelet function in response to these two forms of tobacco use.⁵² This result, combined with the finding that smoking nontobacco cigarettes⁴⁷ failed to produce changes in platelet function as large as observed with tobacco cigarettes, suggests that nicotine is an important active agent. Because nontobacco cigarettes also affected platelet aggregation somewhat, however, carbon monoxide or other combustion products may also influence the platelets.

Sinzinger and Kefalides⁵³ measured platelet sensitivity to antiaggregatory prostaglandins (E_1 , I_2 , and D_2) before, during, and after 15 minutes of exposure to ETS in healthy nonsmokers and smokers. Passive smoking reduced platelet sensitivity to the antiaggregatory prostaglandins I_2 and E_1 significantly ($p < 0.01$) by a factor of about 2 by the end of 15 minutes of exposure to ETS among nonsmokers. This effect persisted at 20 minutes after the end of exposure and ceased by 40 minutes. Platelet response to prostaglandin D_2 changed modestly in a similar pattern but was not significant. Among smokers, the control level of platelet aggregation was higher ($p < 0.01$), and the prostaglandins had no significant effects on platelet aggregation over time during or after exposure to ETS. Sinzinger and Virgolini⁵⁴ also showed that repeated exposure to ETS for 1 hr/day for 10 days produced lasting changes in platelet function in nonsmokers similar to those observed in smokers. Thus, nonsmokers' platelets seem much more sensitive to a single exposure to ETS than do smokers' platelets, and change in platelet sensitivity to disaggregating prostaglandins in nonsmokers exposed to ETS for short periods is similar to that observed in smokers.

Further evidence from the same laboratory that passive smoking increases platelet aggregation comes from work by Burghuber et al.⁵⁵ who studied smokers and nonsmokers who smoked two cigarettes and also exposed a different group of smokers and nonsmok-

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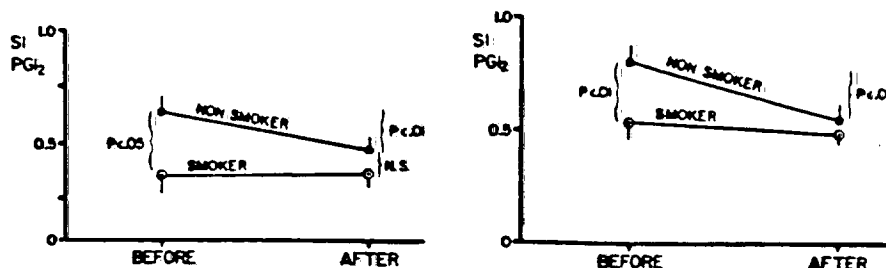


FIGURE 3. Plots of effect of active (left) and passive (right) smoking on platelet aggregation in smokers and nonsmokers. The sensitivity index, $SI\ PGI_2$, is defined as the inverse of the concentration of prostaglandin I_2 necessary to inhibit ADP-induced platelet aggregation by 50%. Lower values of $SI\ PGI_2$ indicate greater platelet aggregation. Adapted from Figures 3 and 4 of Burghuber et al.⁵⁵

ers to ETS in an 18 m³ room in which 30 cigarettes had been smoked just before exposing the nonsmokers. They measured the sensitivity of platelets to the disaggregating substance prostaglandin I_2 that is released by endothelium and inhibits platelet aggregation. Figure 3 shows the results of this experiment. In smokers, neither smoking nor passive smoking affected the sensitivity of the platelets to the disaggregating effect of prostaglandin I_2 . The sensitivity of platelets in smokers was also significantly lower than that of nonsmokers. In contrast, platelets were more sensitive to prostaglandin I_2 in nonsmokers, with both smoking and passive smoking producing a similar reduction in platelet sensitivity to prostaglandin I_2 . These results suggest that the platelets of smokers are already desensitized to the antiaggregatory substance prostaglandin I_2 , so that no further decrease in aggregation is seen. The significant decrease in platelet sensitivity to prostaglandin after short-term exposure to ETS suggests that after ETS exposure platelets are more likely to aggregate with adverse consequences.

Earlier work by Saba and Mason⁵⁶ also indicated that nicotine increased a variety of measures of platelet aggregation in nonsmokers and smokers. Although the *in vitro* effects of nicotine on platelets from smokers was greater than that in nonsmokers, the effect generally did not vary with dose (between 2×10^{-9} and 2×10^{-4} M), suggesting that the effects of nicotine on platelets occur at low doses and that the system saturates quickly. This observation may explain why passive and active smoking have such similar effects on platelets.^{51,52,55}

The probable link between nicotine and adverse physiological effects is nicotine-induced release of catecholamines. Catecholamines are then responsible for increased platelet aggregation. This reasoning suggests that β -adrenergic receptor blockers may provide some protection in smokers. This premise is borne out by a trial comparing the effects of the β -blocker metoprolol to a thiazide diuretic in the control of moderate hypertension.⁵⁷ For the same reduction in blood pressure, the metoprolol-treated group had a significantly lower mortality rate than did the thiazide-treated group. Practically all of this

reduction in mortality, however, was seen in smokers and not nonsmokers. This study provides evidence that blocking the effects of catecholamines (released by nicotine) was the cause of the reduced mortality in smokers who were receiving metoprolol.

In sum, passive smoking increases platelet aggregation, with a magnitude similar to that observed in active smoking. Moreover, the response of nonsmokers to both active and passive smoking appears to be different from smokers, with nonsmokers being more sensitive to lower exposures to cigarette smoke than are smokers. This observation indicates that the pharmacology of ETS in nonsmokers may be different than in smokers, with nonsmokers being more sensitive to low doses of ETS. In particular, it invalidates attempts to estimate "cigarette equivalent" doses of ETS in nonsmokers or extrapolating from risks of smoking in smokers to effects of ETS on nonsmokers.⁵⁸ The resulting increase in platelet aggregation can contribute to acute thrombus formation and myocardial infarction.

In addition to the role of platelets in acute thrombus formation, platelets are also important in the development of atherosclerosis.⁴⁶ Once there is damage to the arterial endothelium, either through mechanical or chemical factors, platelets interact with or adhere to subendothelial connective tissue and initiate a sequence that leads to atherosclerotic plaque. When platelets interact with or adhere to subendothelial connective tissue, they are stimulated to release their granule contents. Endothelial cells normally prevent platelet adherence because of the nonthrombogenic character of their surface and their capacity to form antithrombotic substances such as prostacyclin. Once the endothelial cells have been damaged, the platelets can stick to them. Once the platelets are bound to the endothelium, they release mitogens such as platelet-derived growth factor, which encourage migration and proliferation of smooth muscle cells in the region of the endothelial injury.⁵⁹ If platelet aggregation is increased because of exposure to ETS, the chances of platelets building up at an endothelial injury will be increased. Thus, in addition to contributing to short-term effects through increasing the likelihood of thrombus formation, the

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effects of ETS on platelets also increase the chances that endothelial injury will lead to arterial plaque.

ETS also plays a role in causing damage to the endothelium and initiating the atherosclerotic process. As discussed above, Davis et al⁵¹ found that short-term exposure to ETS, like active smoking⁴⁷⁻⁵⁰ and use of chewing tobacco,⁵² leads to a significant increase ($p < 0.002$) in the appearance of anuclear endothelial cell carcasses in the blood of people exposed to ETS (or tobacco product) constituents. The appearance of these cell carcasses indicates damage to the endothelium, which is the initiating step in the atherosclerotic process. As noted above, the appearance of endothelial cells after passive smoking is almost as great as after primary smoking (Table 2). Exposure to ETS has been shown to produce injuries similar to those observed with exposure to primary smoke and also affects platelets in a way that increases the chances that they will bind to the injured area and promote growth of smooth muscle cells.⁴⁶

Role of the Polycyclic Aromatic Hydrocarbons in ETS

Many atherosclerotic plaques in humans are either monoclonal or possess a predominantly monoclonal component,⁴⁰ which indicates that the smooth muscle cells of each plaque have a predominant cell type. Several animal studies have also shown that injections of polycyclic aromatic hydrocarbons (PAHs), in particular 7,12-dimethylbenz(a,h)anthracene (DMBA) and benzo(a)pyrene,⁶¹⁻⁶⁵ accelerate the development of atherosclerosis. Benzo(a)pyrene is an important element in ETS.¹ The effects of PAHs or other carcinogenic or mutagenic elements in ETS⁶⁶ relate directly to the response to injury theory of atherogenesis discussed above.⁴⁶ Changes in the underlying smooth muscle stimulated by these agents can then initiate the "injury" that leads to platelet aggregation and plaque formation. Thus, long-term exposure to ETS can affect plaque formation through mechanisms similar to those by which long-term exposures produce cancer in other organs.

Albert et al⁶¹ gave chickens weekly intramuscular injections of DMBA and benzo(a)pyrene for up to 22 weeks, then killed the chickens at various times beginning after 13 weeks and measured the plaque volume in the chickens' aortas. They found that both DMBA and benzo(a)pyrene significantly increased the volume of plaque compared with control chickens who had just received injections of the solvent used to carry these agents. This study provided the first evidence that known carcinogenic chemicals can be atherogenic as well.

Penn et al⁶³ extended this result in a similar experiment by showing that the effects of DMBA on the extent of plaque buildup in chickens was dose dependent. The median cross-sectional area of plaques on individual aortic segments and the plaque volume index (an approximate measure of the total volume of plaque per aorta) increased in a nearly linear fashion with DMBA dose. In contrast to the marked increase in plaque area in the DMBA-

treated animals, the percentage of aortic sections with plaques in carcinogen-treated animals was only slightly higher than in controls. Plaques with a small cross-sectional area were present in all animals. Lesions of widely differing cross-sectional areas appeared to be similar histologically under the light microscope.

Together, these data suggest strongly that a major effect of long-term DMBA exposure is to increase the size of spontaneous aortic lesions. Rather than inducing a cancerlike change in an individual cell that begins the process that ultimately leads to plaque formation, Penn et al⁶³ suggested that long-term DMBA exposure causes preferential division of individual cells or patches of cells within the preexisting spontaneous lesions. From this perspective, DMBA and other exogenous compounds would be acting as a mitogen, similar to that released by activated platelets, to stimulate division of aortic smooth muscle.

Revis et al⁶² found similar results in White Carneau pigeons injected with DMBA and benzo(a)pyrene weekly for 6 months, beginning when the pigeons were 3 months old. Compared with the work described above, they found that benzo(a)pyrene had a greater effect on atherogenesis than did DMBA, and they also failed to observe a dose-response relation between the dose given and the amount of aortic plaque. These differences from the work just described may be related to species differences, differences in the carrier used to inject the PAHs (dimethyl sulfoxide in the previous studies compared with corn oil in this one), or differences in the age of the pigeons or dosing schedule. They also found an increase in aortic plaques in pigeons treated with the PAH 3-methylcholanthrene but not the carcinogen 2,4,6-trichlorophenol or the PAH benzo(e)pyrene, which is not considered a carcinogen. This result suggests that carcinogenic PAHs, rather than carcinogens or PAHs in general, are implicated in the atherosclerotic process.

Revis et al⁶² also studied the distribution of these compounds after they had been radiolabeled. Forty-eight hours after the injection of PAHs, radioactivity in the liver, aorta, and lung accounted for 75% of the injected dose, whereas in animals injected with 2,4,6-trichlorophenol, radioactivity in the liver and kidney accounted for 80% of the dose. In addition, 80% of the radioactivity observed in the plasma immediately after injection of radiolabeled PAHs was associated with the low density and high density lipoprotein cholesterol fractions compared with only 24% of the 2,3,6-trichlorophenol, suggesting that plasma lipoproteins are an important vehicle for transporting PAHs to their sites of activation in the arteries.

There is also evidence that ETS directly affects plasma lipoproteins. Moskowitz et al³⁸ showed that adolescent children whose parents smoked had elevated levels of cholesterol and depressed levels of high density lipoproteins, even after correcting for age, weight, height, and sex. These effects were dose dependent; the greater the exposure to ETS, the

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greater were the changes in these variables. Pomeroy et al.¹⁷ observed similar effects of ETS on high density lipoprotein in children whose parents smoked and in children who smoked or chewed tobacco themselves. High levels of total cholesterol and low levels of high density lipoprotein are important for the development of plaque. Data on total cholesterol and high density lipoprotein from non-smokers married to smokers are inconclusive.^{10,14}

To further elucidate the possible mechanisms by which PAHs induce atherosclerotic changes, Majesky et al.¹⁵ administered a single injection of benzo(a)pyrene to White Carneau and Show Racer pigeons, then looked for metabolites of the benzo(a)pyrene in aortic and hepatic tissues 48 hours later. White Carneau pigeons typically develop severe atherosclerosis by 3 years of age, whereas Show Racer pigeons are relatively resistant to aortic atherosclerosis. Aortic preparations of the White Carneau strain exhibited a much greater inducibility of the microsomal monooxygenase system than did those of the Show Racer strain, particularly in young pigeons. Aortic tissues from White Carneau pigeons aged 6–12 months exhibited a threefold to 12-fold inducibility, whereas aortic tissues from the same strain at 2–5 years of age exhibited only minor (maximum, 3.3-fold) and, for the most part, statistically insignificant increases. No age differences in inducibility could be detected in the Show Racer strain. Interestingly, the differences in inducibility manifest in aortic tissues were greater in aortic tissues than in hepatic tissues from the same birds. Thus, the PAHs seem to accelerate any preexisting tendency to develop atherosclerosis.

Regardless of the ultimate mechanism by which PAHs exhibit atherogenic effects, it seems logical to suppose that the reactive intermediary metabolites of these chemicals are the proximate atherogenic or coatherogenic agents because the parent compounds are relatively inert both chemically and biologically. Thus bioactivation and inactivation (and regulatory control of these processes) may be presumed to play extremely important roles in their atherogenic properties. Bioactivated chemicals vary in their stability and reactivity according to four general categories: 1) those that are extremely unstable and persist only at the immediate site (enzyme) of bioactivation, 2) those that persist only within cells in which bioactivation occurs, 3) those that persist primarily only within tissues in which bioactivation occurs, and 4) those capable of being transferred in the circulation from one organ to another. For the first three of these four categories, biotransformation in the aorta *per se* (target tissue activation) would be of prime interest and importance. Thus, it appears that PAHs could be playing either a mutagenic or mitogenic role in beginning the atherosclerotic process in susceptible cells or individuals, depending on how the PAHs in ETS are metabolized in the aorta.

The finding that enzymes that metabolize DMBA and benzo(a)pyrene are in the artery wall led Penn et al.¹⁶ to search for specific molecular events in plaque

cells that would lead to DNA changes similar to those previously found in tumors. Identification of such processes would be supportive of the monoclonal hypothesis of atherogenesis. They obtained human DNA samples from coronary artery plaques as well as DNA from normal sections of the coronary arteries at surgery to remove the plaque. These DNA samples were tested with the NIH 3T3 cell transfection assay. Foci arose in cells transfected with each of the DNA samples obtained from the human coronary plaque, with an efficiency (number of foci/ μ g of DNA) ranging from 0.016 to 0.060 (mean, 0.036). The transfection efficiencies for DNA from normal coronary artery, liver, spleen, lung, kidney, and trachea were all less than 0.008. The transformed cells were also injected into the scalps of nude mice, where they developed tumors. These results provide direct evidence for similarities on the molecular level in the development of plaques and tumors. Human coronary artery plaque DNA contains sequences capable of transforming NIH 3T3 cells, and these transformed cells can cause tumors after injection into nude mice. Control experiments verified that the transforming cells did indeed contain human DNA and that the tumorigenic (or transforming) activity was not due to the *ras* oncogene family. Although these results clearly demonstrate that human plaque DNA has transforming ability, the temporal expression of this activity *in vivo* is not known. The plaques were taken from adult patients in late stages of vascular disease. Thus, we cannot determine from these samples whether the manifestation of transformation is a relatively late event in plaque development or an early but stable event. Oncogene activation and expression is an important early event in transformation and tumor genesis. These results identify specific molecular events that may underlie the proliferation of smooth muscle cells that is a hallmark of atherosclerotic plaque development and demonstrates that plaque cells exhibit molecular alterations that had previously only been thought to be present in cancer-cell transformation and tumorigenesis. These results provide direct support for the monoclonal hypothesis.

Randerath et al.¹⁸ also demonstrated that constituents of cigarette "tar," including benzo(a)pyrene, are preferentially attracted to the heart and damage DNA there. They studied molecular mechanisms of smoking-related carcinogenesis by examining the induction and distribution of covalent DNA damage in internal organs of the mouse after topical application of cigarette smoke condensate daily for 1, 3, or 6 days then killed 24 hours later. DNA samples were obtained from skin, lung, heart, kidney, liver, and spleen. Adducts containing benzo(a)pyrene-derived moieties were identified, together with others. At all three times, the number of adducts in heart and lung DNA was about five times higher than that in liver and slightly higher than that in skin. Covalent DNA damage was estimated to be 6.2, 5.7, 3.9, and 1.9 times higher, respectively, in lung, heart, skin, and

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kidney than in liver, ranging from approximately 1 adduct/ 5.4×10^6 DNA nucleotides in lung to 1 adduct/ 3.3×10^7 DNA nucleotides in liver. Spleen DNA was practically adduct free. Although the DNA adduct profiles resembled each other qualitatively among the different tissues, there were major quantitative differences between the different tissues, with the highest DNA binding occurring in the lung and heart. The reasons for the high incidence of DNA adducts in the heart are not known but may be related to the role of plasma lipids in transporting PAHs such as benzo(a)pyrene and binding of these lipids to coronary arteries.

In sum, there is a growing body of evidence at a molecular level supporting the monoclonal hypothesis of atherogenesis, with compounds in tobacco smoke and ETS strongly implicated as agents that stimulate the development of coronary lesions. Regardless of whether the monoclonal hypothesis proves to be true (or, more likely, one of several initiations of the atherosclerotic process), there is clear evidence that components of ETS, in particular PAHs such as benzo(a)pyrene, initiate or accelerate the development of plaque. These biochemical findings are consistent with the epidemiological finding that chimney sweeps, who are exposed to high levels of PAHs in soot, have an increased risk of heart disease (as well as cancer) and tend to develop these diseases earlier than do members of other, comparable, occupations that are not exposed to PAHs.⁶⁰ The PAHs in ETS are clearly implicated at epidemiological, physiological, and biochemical levels in the genesis of heart disease.

Summary

The evidence that ETS increases risk of death from heart disease is similar to that which existed in 1986 when the US Surgeon General concluded that ETS caused lung cancer in healthy nonsmokers.¹ There are 10 epidemiological studies, conducted in a variety of locations, that reflect about a 30% increase in risk of death from ischemic heart disease or myocardial infarction among nonsmokers living with smokers. The larger studies also demonstrate a significant dose-response effect, with greater exposure to ETS associated with greater risk of death from heart disease.

These epidemiological studies are complemented by a variety of physiological and biochemical data that show that ETS adversely affects platelet function and damages arterial endothelium in a way that increases the risk of heart disease. Moreover, ETS, in realistic exposures, also exerts significant adverse effects on exercise capability of both healthy people and those with heart disease by reducing the body's ability to deliver and utilize oxygen. In animal experiments, ETS also depresses cellular respiration at the level of mitochondria. The polycyclic aromatic hydrocarbons in ETS also accelerate, and may initiate, the development of atherosclerotic plaque.

Of note, the cardiovascular effects of ETS appear to be different in nonsmokers and smokers. Non-

smokers appear to be more sensitive to ETS than do smokers, perhaps because some of the affected physiological systems are sensitive to low doses of the compounds in ETS, then saturate, and also perhaps because of physiological adaptations smokers undergo as a result of long-term exposure to the toxins in cigarette smoke. In any event, these findings indicate that, for cardiovascular disease, it is incorrect to compute "cigarette equivalents" for passive exposure to ETS and then to extrapolate the effects of this exposure on nonsmokers from the effects of direct smoking on smokers.

These results suggest that heart disease is an important consequence of exposure to ETS. The combination of epidemiological studies with demonstration of physiological changes with exposure to ETS, together with biochemical evidence that elements of ETS have significant adverse effects on the cardiovascular system, leads to the conclusion that ETS causes heart disease. This increase in risk translates into about 10 times as many deaths from ETS-induced heart disease as lung cancer; these deaths contribute greatly to the estimated 53,000 deaths annually from passive smoking.⁵ This toll makes passive smoking the third leading preventable cause of death in the United States today, behind active smoking⁷⁰ and alcohol.⁷¹

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KEY WORDS • atherosclerosis • benzo(a)pyrene • carbon monoxide • environmental tobacco smoke • myocardial infarction • passive smoking • platelets • polycyclic aromatic hydrocarbons • secondhand smoke • tobacco smoke pollution • epidemiology • mitochondria

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Passive Smoking and the Risk of Heart Disease

Kyle Steenland, PhD

Objective.—This paper reviews the evidence that exposure to environmental tobacco smoke (ETS) increases the risk of heart disease death among persons who have never smoked (never-smokers). The annual number of heart disease deaths in the United States attributable to ETS is estimated, as is the individual risk of heart disease death for exposed never-smokers.

Data Sources.—Nine epidemiologic studies and numerous experimental studies are available to evaluate the association of ETS and heart disease.

Data Synthesis.—The relative risk for never-smokers living with current or former smokers, compared with never-smokers living with nonsmokers, has ranged from 0.9 to 3.0 in nine studies. Seven studies were positive, one was positive for women but not men, and one was negative. Several studies have shown a dose-response relationship and have controlled for other risk factors. Evidence from experimental studies suggests that ETS can damage the cardiovascular system, via both short-term and long-term mechanisms. Assuming that the observed heart disease risk for those exposed to ETS is not an artifact of misclassification or confounding, approximately 35 000 to 40 000 deaths from ischemic heart disease among never-smokers and long-term former smokers are estimated to have occurred annually in the United States as a result of ETS exposure in the early 1980s. An individual male never-smoker living with a current or former smoker is estimated to have an approximately 9.6% chance of dying of ischemic heart disease by the age of 74 years, compared with a 7.4% chance for a male never-smoker living with a nonsmoker. The corresponding lifetime risks for women are 6.1% and 4.9%.

Conclusions.—The public health burden due to ETS exposure is likely to be much greater for heart disease than for lung cancer, which has been the focus of most debate to date. Individual lifetime excess risks of heart disease death due to ETS of one to three per 100 can be compared with much lower excess risks of one death per 100 000, which are often used in determining environmental limits for other toxins. Exposure to ETS is not currently regulated at the federal level, except for domestic air traffic.

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ENVIRONMENTAL tobacco smoke (ETS) has been associated with a variety of diseases, particularly lung cancer. In 1986, the National Research Council¹ estimated that about 3000 lung cancer cases per year among persons in the United States who had never smoked (never-smokers) were attributable to ETS. In 1990, the Environmental Protection Agency published a draft report reaching similar conclusions.² While the lung cancer risk among never-smokers exposed to ETS is well established, a possible risk of heart disease due to ETS is more controversial. Yet the epidemiologic evidence for a heart disease effect has been increasing in the last several years. This article discusses the available data on ETS and heart disease. Based on the assumption that the epidemiologic studies are reasonably accurate, the annual number of deaths in the United States due to ischemic heart disease (IHD) attributable to ETS is estimated, as well as the individual lifetime risk of IHD death due to ETS.

DATA ON ETS EXPOSURE

Environmental tobacco smoke is difficult to measure directly. Indirect measures that have been used are airborne respirable suspended particulate (defined as particles of less than 2.5- μ m diameter) and urinary cotinine (a metabolite of nicotine). Passive monitors

of vapor-phase nicotine are a promising new direct method to measure ETS.³

Repace⁴ has shown that the background level of respirable suspended particulate (approximately 20 μ g/m³) doubles in homes in which a smoker lives. ETS exposure also occurs outside the home. Approximately 28% of the US adult population smokes, and ETS exposure occurs in most indoor environments. Cummings et al⁵ have shown that 91% of 663 nonsmokers had cotinine in their urine, including 81% of the 162 subjects who reported no exposure to ETS in the previous 4 days (the relevant period for cotinine measurement). The average level of cotinine in the urine of nonsmokers was about 8 ng/mL, compared with about 1200 ng/mL in smokers. Other investigators^{6,7} have shown that nonsmokers living with smokers have 2.5 to 3 times the level of urinary cotinine compared with that of nonsmokers living with nonsmokers.

The relative contribution of ETS exposure at work to total exposure is not well known. Nonsmoking restaurant workers (perhaps a worst case for occupational ETS exposure) averaged 56 ng/mL of urinary cotinine in one study.⁸ Conversely, Haley et al⁹ have shown in a limited sample that urinary cotinine for those exposed at home and at work increased only slightly compared with those exposed only at home.

The National Research Council¹ concluded that nonsmokers exposed to passive smoke are absorbing the equivalent of 0.1 to 1.0 cigarettes a day, based on urinary cotinine levels. However, the constituents of sidestream smoke are different from those of inhaled mainstream smoke. Sidestream smoke is generated at a lower temperature than mainstream smoke, the particle size is smaller, less of the generated smoke is particulate, and the pH is higher.¹ There are more carbon monoxide and nicotine breakdown products in dilute sidestream smoke than in mainstream smoke. These differences imply that it is difficult to determine the relative toxicity of sidestream smoke vs mainstream smoke. Consequently, arguments inferring ETS

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Table 1.—Heart Disease Among Never-Smokers Due to ETS*

Source	Type and Size	Exposure	Rate Ratio (95% CI) (No. of Observed Deaths)	Comment
Hole et al. ¹¹	12-y follow-up, 3660 men, 4037 women	Living with smoker or ex-smoker in early 1970s (self-report)	2.01 (1.21-3.35) (455)	Adjusted for 3 CV risk factors and social class, dose response
Humble et al. ¹²	20-y follow-up, 513 women aged 40 + y	Living with smoker in 1960 (self-report)	1.59 (0.99-2.57) (76)	Adjusted for 3 CV risk factors, dose response in some strata
Helsing et al. ¹³	12-y follow-up, 4182 men, 14 873 women, aged 25 + y in 1963	Living with smoker or ex-smoker in 1963 (self-report); exposure to ex-smokers given less weight	1.31 men (1.1-1.6) (482) 1.24 women (1.1-1.4) (1539)	Small dose response for women only, adjusted for education
Svendsen et al. ¹⁴	7-y average follow-up for 1245 men, aged 35-37 y, 1973-1982 MRFIT study (high-risk men)	Married to smoker (reported by husband)	1.61 (0.96-2.71) (90)	Positive dose response ($P = .2$), adjusted for 3 CV risk factors and education
Garland et al. ¹⁵	10-y follow-up, 695 women aged 50-79 y in 1972-1974	Married to smoker or ex-smoker (self-report)	2.9† ($P < .1$) (19; only 2 in nonexposed persons)	Age-adjusted positive dose response, small sample makes results unstable
Hirayama ¹⁶	16-y follow-up study, 91 540 women aged 40 + y	Married to smoker or ex-smoker	1.10 (low), 1.31 (high) (No CI) (494)	Significant dose response, low to high exposure
Lee et al. ¹⁷	48 cases, 182 controls, 26 male cases, 22 female cases	First marriage to smoker or ex-smoker (self-report)	1.24 (men), 0.93 (women) (NS)	No dose response for total ETS exposure (not spouse alone); hospital-based
He ¹⁸	34 female cases, 68 controls	Married to smoker for 5 or more y	3.00‡	Positive dose response, hospital-based; lacks details on methods
Dobson et al. ¹⁹	160 female cases, 183 male cases, 715 controls	Self-reported home exposure (time period not defined)	0.97 (men), 2.46 (women)‡	Ex-smokers had elevated risk (1.78 men, 1.48 women); no excess risk for workplace exposure; population-based

*ETS indicates environmental tobacco smoke; CI, confidence interval; IHD, ischemic heart disease; CV, cardiovascular; MRFIT, Multiple Risk Factor Intervention Trial; and NS, not significant. IHD mortality (classified as International Classification of Diseases [ICD] codes 410 through 414) is the end point for all studies except Humble et al.¹² which used all CV deaths (ICD classifications 360 through 456), and Lee et al.¹⁷, He¹⁸, Dobson et al.¹⁹ and Svendsen et al.¹⁴ which used incidence.

†Estimated from data in article.

‡Significant at an undetermined level.

health effects based on known health effects of mainstream smoke (cigarette "equivalency") are not appropriate.

HEART DISEASE AND ETS

Epidemiologic evidence has been increasing that passive smoking at home is related to heart disease among never-smokers. Earlier reviews^{1,9} concluded that the hypothesis associating ETS and heart disease was biologically plausible but that epidemiologic and experimental data were inconclusive.

A review of the recent literature shows that six new epidemiologic studies¹⁰⁻¹⁵ have been published regarding ETS and heart disease. Table 1 summarizes all nine epidemiologic studies.¹⁰⁻¹⁸ Seven are positive, while one is positive for women but not men. The five best-designed and largest studies^{10-12,14,15} are cohort studies; three of the five controlled for the principal cardiovascular risk factors (cholesterol, blood pressure, and obesity), and three showed a positive dose response, while the other two showed a positive dose response for certain subgroups. A recent review of most of these studies¹⁹ concluded that "heart disease is an important consequence of exposure to ETS" and estimated that the excess risk of heart disease for nonsmokers living with smokers was 30%.

The principal weaknesses in the epidemiologic evidence to date have been the indirect methods of assessing exposure (via spousal smoking) and the lack of data on exposures to ETS outside the

home. If the effect of ETS on the coronary system is long-term, early exposures during childhood might also be important, but childhood exposures have not been considered in the epidemiologic studies. Also, there are many risk factors for heart disease, and it is difficult to control well for all of them.

Another problem with the epidemiologic data is the seemingly large effect that ETS has on heart disease compared with the effect of mainstream smoking. Active smoking is associated with heart disease, with a relative risk of smokers vs nonsmokers of about 1.7.²⁰ Most studies of never-smokers living with smokers indicate relative risks on the order of 1.2 to 1.3, compared with those of never-smokers living with never-smokers. These relative risks seem high compared with the risk for mainstream smoking. There are several counterarguments to this objection. Studies of mainstream smokers have used referent groups of never-smokers composed of never-smokers exposed to ETS and never-smokers not exposed to ETS, so that relative risks from mainstream and passive smoking studies are not directly comparable. Another argument is that dosimetry based on cigarette equivalents is misleading, since sidestream smoke is qualitatively different than mainstream smoke, and exposure to sidestream smoke may be proportionately more toxic to the heart than exposure to mainstream smoke.

Due to the relatively slight increased

risk of heart disease for passive smokers and the many factors known to affect heart disease, the possibility of uncontrolled confounding as a cause for the increased risk cannot be ruled out. Confounding by dietary factors might bias disease risks for passive smokers upward. This suggestion is based on findings that never-smokers living with smokers have less nutritious diets than never-smokers living with nonsmokers.^{21,22} The argument has principally been made for lung cancer risk and has focused on food containing carotenoids or retinoids, which are protective against lung cancer. A similar argument might be made for heart disease. However, several of the heart disease studies have adjusted for cholesterol, the most established heart disease risk factor related to diet. Furthermore, in one study,²¹ never-smokers living with smokers ate significantly less cholesterol-containing food than never-smokers living with nonsmokers (while also eating significantly less carotenoid-containing vegetables). While carotenoids and retinoids may be protective against heart disease as they are against lung cancer, little published data support this claim.

An increasingly substantial body of animal and human experimental evidence supports the hypothesis that ETS increases the risk of heart disease. The 1986 National Research Council report noted that levels of carboxyhemoglobin (COHb) among those highly exposed to ETS was reported to be close to 3% and also noted

that animal and theoretical models suggested such levels might have adverse effects on the heart. However, the National Research Council found little evidence that ETS exposure in healthy subjects was detrimental. Since 1986 a series of new experimental studies have been reviewed by Glantz and Parmley,¹³ who cite human evidence that ETS exposure (1) increases COHb and adversely affects exercise performance in both heart patients and healthy individuals; (2) increases platelet aggregation (at levels slightly less than those seen in active smokers) and adversely affects platelet function; and (3) damages the arterial endothelium (again at levels slightly less than those seen in active smokers). They also cite animal evidence that components of ETS (eg, polycyclic aromatic hydrocarbons) can increase the risk of atherosclerotic plaques. Hence, ETS might be thought to have either short-term effects on the heart (via COHb or thrombosis) or long-term effects (via endothelial damage and plaque development).

Two new human experimental studies lend further support to the adverse effect of ETS on the heart. Allred et al¹⁴ studied 63 nonsmoking men with heart disease tested on a treadmill, after exposure to room air or to air with carbon monoxide levels of 117 ppm or 253 ppm (resulting in COHb levels of 0.6%, 2.0%, and 3.9%, respectively). The time to angina onset decreased significantly by 4.2% and 7.1% in those exposed to low and high carbon monoxide levels, respectively, compared with those exposed to room air. Sheps et al¹⁵ studied 41 nonsmokers with coronary artery disease to assess the effects of carbon monoxide on ventricular arrhythmias. Patients performed a baseline bicycle exercise test and were exposed to room air (1.5% COHb), 100 ppm carbon monoxide (4% COHb), and 200 ppm carbon monoxide (6% COHb) over 3 days, followed by more exercise. Those with 6% COHb had significantly more arrhythmias during exercise than those exposed to only room air. When arrhythmias were weighted by severity, a dose response was observed.

The above experimental findings among heart patients exposed to carbon monoxide find epidemiologic support from a study of men exposed to high levels of carbon monoxide while working in New York City tunnels.¹⁶ These men, exposed to carbon monoxide levels of approximately 50 ppm, suffered a 35% excess of IHD mortality compared with the US population, an excess that declined sharply after employment cessation (indicating a short-term effect). They showed no excess of lung cancer, and cross-sectional smoking data revealed smoking habits similar to the US referent population.

Hence, increased cigarette smoking was unlikely to explain the excess heart disease risk.

Finally, recent evidence from two studies shows that exposure to ETS may lower levels of high-density lipoprotein cholesterol (HDL-C) and increase fibrinogen. Active smoking lowers HDL-C.¹⁷ A recent study of never-smoking adults showed that those with ETS exposure (measured by urinary cotinine) had significantly lower HDL-C levels than adolescents without ETS exposure (7% lower) and significantly higher ratios of total cholesterol to HDL-C.¹⁸ Another cross-sectional study¹⁹ found higher levels of fibrinogen in nonsmokers exposed to ETS vs nonexposed nonsmokers. The authors suggested that higher fibrinogen levels might lead to increased thrombogenesis. While these studies were not longitudinal and provided evidence of a correlation but not causation, the data suggest other mechanisms by which ETS may contribute to cardiovascular disease.

In summary, recently published experimental and epidemiologic studies strengthen the case for a true association of ETS exposure and heart disease.

RISK ASSESSMENT

Risk assessment often means the development of a mathematical model to predict risks of disease based on a given quantified dose or exposure. Frequently, animal data are used, with doses well quantified. Assumptions are then required regarding the application of animal data to humans. Occasionally, epidemiologic (human) data are available with sufficient quantitative detail on exposure to permit such a risk assessment, but more often the data on exposure are qualitative (eg, exposed vs nonexposed), so that no quantitative dose response can be estimated. This is the case for ETS. However, two other types of risk assessment remain possible for ETS.²⁰

The type used in this article is based on the epidemiologic literature and on the observed relative risk for never-smokers exposed to ETS vs those nonexposed. This type of risk assessment can be used to estimate the annual number of deaths due to ETS exposure among never-smokers in the United States. The excess lifetime risk for an individual never-smoker due to exposure to ETS (at an unknown average dose) beyond the background risk of a never-smoker with no ETS exposure can also be calculated. The most important assumption in this type of risk assessment is that there indeed is a real increase of risk for never-smokers exposed to ETS compared with those not exposed and that this increase in risk can be estimated from the existing epidemiologic studies.

The estimates of population and individual risks are crude, but they provide a sense of the public health burden of heart disease due to ETS exposure.

Another method of risk assessment relies on models predicting the risk of mainstream smokers for heart disease by number of cigarettes smoked, and then estimates the equivalent number of cigarettes absorbed by nonsmokers exposed to ETS. However, this "dosimetric" method depends on too many assumptions about what is a "cigarette-equivalent dose" for those exposed to ETS, and so is not used here.

Presented herein are estimates of the number of IHD deaths due to ETS exposure among never-smokers, among former smokers who have quit 15 or more years previously, and among former smokers who quit 5 or more years previously. After quitting, smokers have a sharp reduction in heart disease risk (an estimated 50% in the first year), followed by a long decline in risk (a reduction in the long-term and presumably atherogenic effect), until reaching approximately the same risk as never-smokers after 15 years.²¹ Hence, long-term former smokers (those who have not smoked for 15 or more years) can reasonably be considered as never-smokers. Former smokers with fewer years since quitting will have an increased risk from both ETS and their previous mainstream smoking, but the epidemiologic data to date do not permit a separation of these effects. Herein are calculated the ETS-attributable heart disease deaths for former smokers who quit 5 or more years previously, and it is assumed that the true number of ETS-attributable heart disease deaths for all former smokers lies somewhere between the attributable deaths for long-term former smokers (15 or more years) and short-term former smokers (5 or more years).

Current smokers are not considered here. Any additional IHD risk due to ETS exposure for current smokers is likely to be small compared with the effect of their mainstream smoking.

US DEATHS ATTRIBUTABLE TO IHD ANNUALLY

Formulas for Attributable Deaths

As shown in formula 1 below, the deaths attributable to IHD among never-smokers is

$$(EF)(d) = (EF)(I)(N),$$

where EF is the age-specific etiologic fraction, d is the age-specific number of IHD deaths among US never-smokers, I is the age-specific mortality rate from IHD among US never-smokers, and N are the age-specific person-years at risk

for US never-smokers.

The etiologic fraction is an epidemiologic measure to estimate the proportion of disease due to a specific exposure, based on the proportion of the population exposed and the relative risk due to the exposure.²⁰ In the context of passive smoking, it is defined²⁰ in formula 2 below as

$$EF = \frac{p(RR_1 - 1) + (1 - p)(RR_2 - 1)}{p(RR_1 - 1) + (1 - p)(RR_2 - 1) + 1}$$

Here, p is the fraction of never-smokers exposed to ETS at home (living with a smoker), RR_1 is the rate ratio for never-smokers exposed to ETS at home vs never-smokers not exposed to ETS (the truly nonexposed), RR_2 is the rate ratio for never-smokers exposed to ETS at work or in social settings but not living with a smoker vs never-smokers not exposed to ETS (the truly nonexposed).

Derivation of RR_1 and RR_2

The RRs for IHD for never-smokers (1.31 for men and 1.24 for women) living with current or former smokers are from the study by Helsing et al.¹⁰ the choice of which is dictated by several reasons. The goal here is to estimate the impact of ETS in the United States (other countries often have different types of tobacco and consumption patterns). The Helsing study is the only US study of IHD deaths in a large general population of both men and women. The study results are similar to the approximate results for all ETS-heart disease studies combined.¹⁹ Choosing a point estimate of effect from a meta-analysis of all studies would yield about the same result. The Helsing study considered as exposed those never-smokers living with current smokers or ex-smokers, and hence assumes that heart disease can result from current exposure (a short-term effect) or past exposure (a long-term effect) from ETS. This definition of exposure is the one used in most studies of ETS and heart disease.

Two adjustments were made to these RRs prior to their use in formula 2 above, following the methods outlined by Wald et al.²¹ The first adjustment is for the possibility that some people (approximately 7%) have been misclassified as never-smokers, but are current or former smokers. Such misclassification is potentially a serious problem. However, for heart disease this adjustment has little effect, largely because the heart disease RR for smokers compared with that for nonsmokers is relatively low (about 1.7). As a result of the adjustment, the RR for never-smoking men exposed to ETS decreased from 1.31 to 1.29, while the RR of 1.24 for women decreased to 1.22.

Table 2.—Attributable Deaths for Never-Smokers*

Sex and Age Group, y	US Population Never-Smokers, 1978-1980	IHD Rate per 100 000 Never-Smokers	Etiologic Fraction (Formula 2)	IHD Deaths Due to ETS† (Formula 1)
Women				
30-44	20 050 994	1.8	.2048	74
45-64	11 403 101	32.8	.2048	766
65+	9 748 043	921.3	.2048	18 390
Men				
30-44	13 748 652	2.8	.1900	73
45-64	4 564 316	181.7	.1900	1402
65+	3 086 316	1248.4	.1900	7321
Total				28 026

*IHD indicates ischemic heart disease; and ETS, environmental tobacco smoke. The text contains details of the formulas noted.

†These numbers are the products of the data in the second, third, and fourth columns.

The second adjustment has a greater effect and adjusts for background ETS exposure outside the home. The referent group of never-smokers living with nonsmokers was not truly nonexposed to ETS. It can be assumed that the referent group had an unknown increased rate of disease (b) compared with those truly nonexposed to any ETS. Never-smokers living with smokers showed about three times the cotinine as those living with nonsmokers.⁷ If the increased rate of disease for never-smokers living with smokers should be about three times ($3b$) that of never-smokers living with nonsmokers but exposed to ETS outside the home (b), then according to formula 3,

$$\text{Observed } RR = 1 + 3b/1 + b.$$

Solving for b and using an observed RR of 1.29 for men, for male never-smokers living with smoking spouses, the RR for IHD death compared with that for never-smokers with no exposure to ETS (no exposure at home, work, or social settings) is 1.51, while the RR for male never-smokers not living with smoking spouses but exposed to background ETS at work or in social settings is 1.17 ($b = .17$). The corresponding RRs for women are 1.37 and 1.12. These adjusted RRs are used in the calculation of the etiologic fraction (formula 2 above).

The Fraction of Never-Smokers Living With Smokers

To calculate this fraction (the p in formula 2), data are taken from the never-smoking controls in four US case-control studies of lung cancer and ETS, conducted in the late 1970s and early 1980s.²²⁻²⁵ These studies involved 658 men and 878 women, of whom 19% and 55% had spouses who were smokers or ex-smokers. Age-specific exposure prevalence was not available from these studies. Age-specific data from 778 female controls in a recent US lung cancer case-control study (Elizabeth Fontham, PhD,

written communication, July 1991) tend to confirm the overall estimate for women and show little difference in the percentage exposed after the age of 45 years.

Approximately 75% of US adults are married.²⁶ The assumption made here is that the married and unmarried individuals are alike regarding their potential for exposure to ETS. Some data justify this assumption, based on urinary cotinine levels of single women.²

IHD Rates Attributable to ETS

Age-specific (at 5-year intervals) and sex-specific IHD rates for US never-smokers were estimated using data from four cohort studies: (1) the cohort study conducted by the American Cancer Society²⁶ (follow-up 1982 through 1985) (Lawrence Garfinkel, MA, American Cancer Society, written communication, June 1990); (2) the US veterans cohort study²⁷ (follow-up 1975 through 1980, men only) (Aaron Blair, PhD, National Cancer Institute, written communication, June 1991); (3) the Seventh-Day Adventist cohort study²⁸ (follow-up 1977 through 1982) (Paul Mills, PhD, Loma Linda University, written communication, June 1991), and the Nurses Health Study²⁹ (follow-up 1976 through 1988, women only) (Graham Colditz, MD, Nurses Health Study, written communication, July 1991). To combine these rates, unweighted averages (three studies per sex) were taken of the age- and sex-specific rates, and direct standardization (with the 1980 US population as the standard) was used to create summary rates for the three age categories in this review (<45, 45-64, 65+ years).

Estimates of the age- and sex-specific number of never-smokers in the United States were obtained from the 1978 through 1980 National Health Interview Surveys³⁰ (and Robert Brackbill, PhD, National Institute for Occupational Safety and Health, written communication, April 1991).

Table 3 — Attributable Deaths for Former Smokers*

Sex and Age Group, y	US Population of Former Smokers (%)	IHD Rate per 100 000 Never-Smokers	Etiologic Fraction (Formula 2)	IHD Deaths Due to ETS† (Formula 1)
Smokers Quitting 15 or More Years Previously				
Women				
30-44	423 586 (7)	1.8	.2048	2
45-64	1 126 576 (28)	32.8	.2048	76
65+	709 214 (36)	921.3	.2048	1336
Men				
30-44	781 003 (10)	2.8	.1900	4
45-64	1 924 411 (28)	161.7	.1900	591
65+	2 114 671 (36)	1248.4	.1900	5016
Total				7027
Smokers Quitting 5 or More Years Previously				
Women				
30-44	2 440 161 (41)	1.8	.2048	9
45-64	2 802 232 (66)	32.8	.2048	175
65+	1 338 545 (69)	921.3	.2048	2525
Men				
30-44	3 671 518 (46)	2.8	.1900	19
45-64	4 709 367 (70)	161.7	.1900	1447
65+	3 512 504 (78)	1248.4	.1900	8332
Total				12 507

*IHD indicates ischemic heart disease; and ETS, environmental tobacco smoke. The text contains details of the formulas noted.

†These numbers are the product of the data in the second, third, and fourth columns.

Multiplying these rates and population estimates by the etiologic fraction, approximately 28 027 deaths among US never-smokers are estimated to have occurred annually in the 1980s as a result of ETS exposure (Table 2).

Similar data for former smokers who quit 15 or more years previously are summarized in Table 3, based on the assumption that they have approximately the same relative risk and proportions exposed as never-smokers. Also presented are attributable deaths under the assumption that former smokers who quit 5 or more years previously have the same risks from passive smoking as do never-smokers. These last data indicate how attributable deaths increase under a variety of assumptions about the return of former smokers to baseline (never-smoker) risk. The final estimates of attributable deaths are presented as a range, assuming that the true number of ETS-attributable IHD deaths among former smokers lies between the number derived in considering only former smokers who quit more than 15 years previously and the number derived by considering former smokers with 5 or more years since quitting (Table 3). Combining the above estimates, the overall estimate of ETS-attributable heart disease deaths for never-smokers and former smokers is 35 000 to 40 000.

IHD RISK FOR NEVER-SMOKERS LIVING WITH SMOKERS

Individual excess risk of death for a never-smoker exposed to ETS can be derived using an RR estimate and converting rates for never-smokers to a cumulative risk of IHD death by a given

age, using formula 4 below, which accounts for competing causes of death⁴¹:

$$\text{Excess risk} = \sum_{i=20}^{74} (RR_i - 1)q_i(i) \exp \left[- \sum_{j=20}^{i-1} (RR_j - 1)q_j(j) + q_0(j) \right]$$

In formula 4 excess risk refers to cumulative excess risk of IHD death by the age of 74 years, q_i is the IHD mortality rate for nonexposed (truly nonexposed, no ETS exposure in home or elsewhere), q_0 is the overall all-causes mortality rate for the nonexposed (here assumed to be the all-causes mortality rate for never-smokers) (age- and sex-specific data for 1982 through 1984 provided by Lawrence Garfinkel, MA, American Cancer Society, written communication, June 1990), RR is the rate ratio for the exposed vs the nonexposed (assumed to be constant over age), and i and j index ages. Background risk for never-smokers may be calculated by omitting the terms using the RRs. An Axelson-type adjustment⁴² was used to derive the background IHD rate for the truly nonexposed. The Axelson technique consists of partitioning the overall IHD mortality rate for never-smokers into a weighted average of the rate for those with background exposure (the rate for the truly nonexposed times the RR for never-smokers with background ETS exposure) and the rate for those living with smokers (the rate for the truly nonexposed times the RR for never-smokers living with smokers). The resulting equation may then be solved for the rate of those truly nonexposed.

For a female never-smoker with no ETS exposure (truly nonexposed), the lifetime (to an average age of 79 years) risk of IHD death is 4.4%. The risk for a female never-smoker exposed to background ETS exposure is 4.9%, while the risk for a female never-smoker living with a smoker is 6.1%. Corresponding results for men from age 30 to an average age of 74 years are 6.3%, 7.4%, and 9.6%. These results should be viewed as crude estimates, given the multiple assumptions involved. These risks apply to long-term former smokers.

The estimated increased risks of death from IHD due to ETS exposure are higher than those accepted in regulating environmental toxins. For example, environmental limits for toxins are often set to limit the number of excess deaths resulting from exposure to one in 10^5 or one in 10^6 ,⁴³ whereas the excess risks calculated are in the range of one to three per 100. There are currently no federal regulations regarding exposure to ETS, with the exception of regulation for domestic airline flights.

CONCLUSION

A number of assumptions are involved in estimating the heart disease mortality due to ETS, adding an unfortunate level of uncertainty. The most important assumption is that the relative risks for ETS and heart disease, derived from the epidemiologic evidence, are reasonably accurate. The epidemiologic results may be questioned; given the inherent uncertainties of any epidemiologic study. Differential misclassification of ever-smokers as never-smokers and uncontrolled confounding are possible explanations for the excess risk observed in the epidemiologic studies. However, neither of these likely accounts for the observed risks. The epidemiologic data are strengthened because multiple studies now are consistent and reasonably well designed.

Considerable uncertainty is involved in extrapolating from the epidemiologic data, which consider the relative risks for never-smokers living with smokers, to estimating relative risks for those exposed to ETS (anywhere) vs those truly not exposed (anywhere). This latter population of the truly nonexposed is largely hypothetical, in that virtually everyone is exposed to background levels. This extrapolation was made based on observed relative risks for ETS exposure at home and on urinary cotinine measurements, but is necessarily a crude estimate. If it were assumed that background (not from spouse) exposure causes no increase in risk (ie, a threshold effect), then the number of annual IHD-attributable deaths (due solely to

exposure from a spouse) drops to about 15 000 to 19 000.

The above estimate of 35 000 to 40 000 IHD deaths attributable to ETS among never-smokers and former smokers is based on data from the early 1980s. The current number of attributable deaths is likely to be lower, given the declining prevalence of smoking, declining heart disease mortality, and the increased societal trend to limit exposure to ETS.

One prior risk assessment of ETS and heart disease exists, using methods similar to those used here. Wells¹⁴ estimated that in the United States in 1985 there were 32 000 heart disease deaths among nonsmokers (never-smokers and former smokers) attributable to ETS. His estimate is surprisingly close to the one presented herein, despite the fact that he used different data and assumptions in his estimate. Wells included all former smokers in the population at risk for ETS-induced heart disease, while my discussion is restricted to never-smokers and former smokers with at least 5 years since

quitting. Wells extrapolated American Cancer Society data from the 1960s for heart disease rates among never-smokers to estimate these rates for the 1980s. I have used never-smoker heart disease rates from four cohort studies in the 1970s and 1980s. Wells used a different procedure to estimate the prevalence and effect of exposure outside the home.

In this article the assumption has been made that never-smokers living with current or former smokers have an increased risk of heart disease. That is, both short-term and long-term effects of ETS on the heart have been assumed. This assumption agrees with the epidemiologic evidence, which in most studies has defined exposure as living with a current smoker or an ex-smoker. If one were to assume the effect of ETS on the heart were only short-term (eg, via an increase in COHb), then one would have to use RRs from studies in which exposure is defined as living with a current smoker. There are two US studies using this definition of exposure.^{12,16} Both show a higher RR for

exposed vs nonexposed (approximately 1.6) than the one assumed here (1.2 to 1.3). However, these studies have limitations for use in calculating attributable risk. One¹² included only women and the outcome was based on all circulatory disease (including stroke), not IHD. The other¹⁶ included only men at high risk of heart disease.

In conclusion, assuming the epidemiologic evidence is valid and assuming our estimate of 35 000 to 40 000 annual excess heart disease deaths among never-smokers and long-term former smokers due to passive smoking is correct, then heart disease mortality is contributing the bulk of the public health burden imposed by passive smoking. Lung cancer, the previous main culprit, has been estimated to cause approximately 3000 excess deaths per year among never-smokers.

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AHA Medical/Scientific Statement

Position Statement

Environmental Tobacco Smoke and Cardiovascular Disease

A Position Paper From the Council on Cardiopulmonary and Critical Care, American Heart Association

Aubrey E. Taylor, PhD, Chairman; Douglas C. Johnson, MD,
and Homayoun Kazemi, MD, Members

Cigarette smoking was identified by the Surgeon General in 1982 and 1983 as the most important modifiable risk factor for cancer and chronic heart disease in the United States.^{1,2} Recent studies have implicated exposure to environmental tobacco smoke as a significant risk factor for the development of lung cancer and heart disease. Because more information on environmental tobacco smoke is now available, its health effects are reviewed in this report, with a major emphasis on the relation of environmental tobacco smoke to cardiovascular disease.

Cigarette smoking has a significant effect on the health of Americans, and is a major cause of cardiovascular disease.³ Cardiovascular disease attributable to voluntary cigarette smoking accounts for about as many deaths each year as chronic obstructive pulmonary disease and lung cancer deaths combined. In 1988 approximately 430,000 deaths in adults aged 35 and older were attributed to the intentional inhalation of tobacco smoke. This number included 201,000 deaths due to cardiovascular disease, 112,000 due to lung cancers, 83,000 due to chronic lung disease (including pneumonia, influenza, bronchitis, emphysema, chronic airway obstruction, and other respiratory diseases), and 31,000 due to other cancers.⁴ It has also been estimated that an additional 3,800 lung cancer deaths⁴ and 37,000 cardiovascular deaths occurred in nonsmokers who had been exposed to environmental tobacco smoke.⁵ An additional 2,500 perinatal deaths were estimated to have occurred because of maternal smoking, and about 1,300 deaths resulted from burns related to smoking.⁴

Although the existing epidemiological studies on cancer deaths associated with environmental tobacco smoke may be subject to questions about sample size, exposure, experimental design, and differing lifestyles of populations, sufficient information has been published to implicate environmental tobacco smoke as a definite health hazard. The 1986 Surgeon General's report concluded that involuntary smoking is a cause of

disease, including lung cancer, in healthy nonsmokers, and it was postulated that approximately 3,000–4,000 nonsmokers exposed to environmental tobacco smoke die of lung cancer each year.⁶ The report also concluded that children whose parents smoke have an increased frequency of respiratory infections, increased symptoms of respiratory problems,⁷ and slightly smaller rates of increase in lung function as the lung matures compared with children of nonsmoking parents. At the time of the report, environmental tobacco smoke could not be definitely linked to cardiovascular disease. However, since 1986 several studies have been published documenting a link between environmental tobacco smoke, cancer,⁷ and heart disease.^{8,9} The Environmental Protection Agency has also done an extensive study of the effects of environmental tobacco smoke on lung cancer.

Environmental Tobacco Smoke

Burning cigarettes emit two types of smoke: mainstream smoke, which is the smoke directly inhaled into the smoker's lungs, and sidestream smoke, which is the smoke emitted into the air from the burning cigarette between puffs. Environmental tobacco smoke is about 85% sidestream and 15% exhaled mainstream smoke. More than 4,000 chemicals, including at least 40 carcinogens, are contained in environmental tobacco smoke.⁹ Many toxic constituents are found in higher concentrations in sidestream than in mainstream smoke.⁹ For example, in sidestream smoke there is about five times as much carbon monoxide (which decreases the ability of hemoglobin to carry oxygen to the tissues), three times as much benzopyrene (a tumor- and plaque-producing compound), and 50 times as much ammonia (an eye and respiratory irritant) as is inhaled directly from a cigarette. The difference is because the cigarette burns at a higher temperature during inhalation, leading to more complete combustion, and filters also screen some of these toxic compounds.

Those in close proximity to someone smoking a cigarette are exposed to smoke not only while the cigarette is lit but continue to inhale smoke that has mixed with air long after the cigarette is extinguished. Environmental tobacco smoke can persist in indoor environments for many hours after cessation of smoking, the time depending on ventilation and the mixing of

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room air with uncontaminated air.¹⁰ To conserve energy, building ventilation rates are sometimes decreased, causing levels of smoke to increase in workplace environments, and in many homes ventilation of smoke to the outside is minimal.

Risk to Nonsmokers from Environmental Tobacco Smoke

The relative risk of developing lung cancer has been estimated to be 1.3 for nonsmokers exposed to environmental tobacco smoke at home compared with nonsmokers with no exposure to environmental tobacco smoke.^{7,10,12} Active smoking has a relative risk factor for cancer of about 10.¹ Average workplace exposures to environmental tobacco smoke are estimated to increase lung cancer risk twofold because environmental tobacco smoke exposures are generally higher at the workplace than at home.¹² Despite the difficulty of interpreting epidemiological studies of exposure levels in the home and workplace, several recent studies demonstrate a definite link between cardiovascular deaths in nonsmokers exposed to environmental tobacco smoke. Glantz and Parmley³ reviewed 10 of these studies, showing that men and women nonsmokers exposed to environmental tobacco smoke at home had an overall cardiovascular relative risk factor of 1.3. This compares to a relative risk factor of 1.7 for smokers compared with nonsmokers.² Kawachi et al¹³ predicted an even higher relative risk factor for workplace exposures of nonsmokers to environmental tobacco smoke.

Repace and Lowrey⁴ evaluated eight studies in which the number of lung cancer deaths of nonsmokers exposed to environmental tobacco smoke averaged $5,000 \pm 2,400$ (mean \pm standard deviation) per year. Assuming that the ratio of lung cancer to heart disease deaths is the same with environmental tobacco smoke exposure as for voluntary smoking, approximately 10,000 deaths of nonsmokers exposed to environmental tobacco smoke would be expected to occur per year. However, this simple estimate does not include many aspects of environmental tobacco smoke exposure, such as the amount of environmental tobacco smoke exposure in the workplace and home, the number of persons exposed to environmental tobacco smoke, and the type and amount of smoke exposure. In fact, studies to evaluate these factors indicate that environmental tobacco smoke causes a higher risk of heart disease than predicted by this simple estimate.

Recently, Steenland⁸ performed extensive analyses of the available literature on the cardiovascular effects of environmental tobacco smoke and predicted that ischemic heart disease could cause as many as 15,000–19,000 deaths yearly of nonsmokers due solely to environmental tobacco smoke from their spouses. Steenland also predicted an overall number of deaths due to environmental tobacco smoke-related cardiovascular disease of 35,000–40,000 yearly, a number similar to the number of deaths estimated by Glantz and Parmley³ and Wells.¹⁴ Because the risk of coronary artery disease increases markedly with the number of risk factors,^{1,3,15} nonsmokers with hypertension or hypercholesterolemia and exposed to environmental tobacco smoke are likely to be at even greater risk of developing cardiovascular disease. It is well known that the risk of coronary heart disease caused by voluntary smoking decreases by about

half after 1 year of smoking cessation and after several years approaches that of people who have never smoked.¹⁶ Similar health benefits should occur in previously environmental tobacco smoke-exposed nonsmoking individuals when environmental tobacco smoke is removed from the environment in which they work and live.⁸

Exposure to Environmental Tobacco Smoke

Although the proportion of smokers in the United States is decreasing, 32% of men and 27% of women aged 20 and older smoke cigarettes.¹⁷ These smokers will expose a vast number of nonsmokers to environmental tobacco smoke, and it has been estimated that approximately 50 million nonsmoking adults over age 35 are regularly exposed to environmental tobacco smoke.¹⁷ Additionally, we estimate that 50% of all children live in families with one or more smokers. In a survey conducted in 1979–1980, 63% of nonsmokers reported being exposed to environmental tobacco smoke for more than 1 hour per week, 35% were exposed to environmental tobacco smoke for more than 10 hours per week, and 16% were exposed to environmental tobacco smoke for at least 40 hours per week.¹⁸ It is likely that exposure of nonsmokers to environmental tobacco smoke has decreased in recent years because of the increased public awareness of the hazards of environmental tobacco smoke, increased restrictions on smoking areas, and better ventilation of the workplace. The public has now begun to understand the detrimental health effects of environmental tobacco smoke exposure, but this increased awareness has not eliminated exposure to environmental tobacco smoke of spouses and children living in a smoker's home or that occurring in some workplaces and public buildings.

Cardiovascular Effects of Environmental Tobacco Smoke

Environmental tobacco smoke produces acute effects on cardiovascular function in human studies. In subjects with stable angina, environmental tobacco smoke increases resting heart rate, blood pressure, and blood carboxyhemoglobin, and reduces the duration of exercise that induces angina.^{19,20} Environmental tobacco smoke also produces adverse effects on the exercise performance of healthy people.²¹ Several studies have found increases in the incidence of nonfatal heart disease, including angina and myocardial infarction, among nonsmokers exposed to environmental tobacco smoke.^{22,23}

A few small sample cases show direct involvement between environmental tobacco smoke and peripheral vascular disease. For example, Bocanegra and Espinoza²⁴ reported Raynaud's phenomenon in two successive wives of a chain-smoker. The symptoms of both nonsmokers, as would be expected, subsided after they were no longer exposed to environmental tobacco smoke. Cigarette smoking is a major, preventable risk factor that promotes atherosclerotic peripheral vascular disease,^{1,2} and it is likely that environmental tobacco smoke also increases the risk for peripheral vascular disease, although the latter hypothesis remains to be studied.

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Mechanisms of Inducing Cardiovascular Disease

Nicotine, the drug in tobacco that causes addiction, produces acute increases in heart rate and blood pressure.²⁵ Cigarette smoking has been shown to increase platelet aggregation and cause endothelial cell damage.²⁶⁻²⁸ Polycyclic aromatic hydrocarbons present in smoke (for example, benzo[a]pyrene) are capable of inducing and accelerating the development of atherosclerosis.^{29,30} Exposure to environmental tobacco smoke will also increase carbon monoxide levels in red blood cells. Studies indicate that increased carbon monoxide levels in humans result in a more rapid onset of angina³¹ and increased arrhythmias³² in exercising nonsmokers. A recent study indicates that environmental tobacco smoke sensitizes circulating neutrophils in humans and may cause their subsequent activation and oxidant-mediated tissue damage, leading to carcinogenesis and atherosclerosis.³³ It is likely that these and more yet-to-be-identified mechanisms are involved in increasing the risk of heart disease in persons exposed to environmental tobacco smoke.

Potential for Prevention

Although regulation of tobacco products is specifically prohibited under the Federal Hazardous Substances Act, many actions have been taken to protect the health of nonsmokers. For example, cigarette smoking has been banned from air flights in the 48 contiguous states; and as of March 1991, laws restrict smoking in public places in 46 states, in public-sector workplaces in 38 states, and in private-sector workplaces in 17 states.³⁴ Many hospitals, health care facilities, and private and public workplaces are smoke-free. The benefit of restricting smoking in buildings and workplaces is obvious, but the effect of a greater awareness of the importance of reducing environmental tobacco smoke in the home has not been evaluated.

The final conclusion of the 1986 Surgeon General's Report was that separating the smokers and nonsmokers within the same air space may reduce but does not eliminate the exposure of nonsmokers to environmental tobacco smoke. Attempts to control tobacco smoke by increasing room ventilation can be futile, and the only sure way to protect nonsmokers from environmental tobacco smoke is to eliminate smoking from areas that they share with nonsmokers. Environmental tobacco smoke must now be considered an environmental toxin from which the public and workers should be protected. Thus, it is the responsibility of the employer to protect workers, and of public building managers, to protect the public from environmental tobacco smoke exposure. It is the responsibility of parents to ensure that their children are not exposed to environmental tobacco smoke in the home, and the responsibility of everyone to eliminate this health hazard from the environment.⁵

Summary

Although the number of cardiovascular deaths associated with environmental tobacco smoke cannot be predicted with absolute certainty, the available evidence indicates that environmental tobacco smoke increases the risk of heart disease. The effects of environmental tobacco smoke on cardiovascular function, platelet function, neutrophil function, and plaque for-

mation are the probable mechanisms leading to heart disease. The risk of death due to heart disease is increased by about 30% among those exposed to environmental tobacco smoke at home and could be much higher in those exposed at the workplace, where higher levels of environmental tobacco smoke may be present. Even though considerable uncertainty is a part of any analysis on the health affects of environmental tobacco smoke because of the difficulty of conducting long-term studies and selecting sample populations, an estimated 35,000-40,000 cardiovascular disease-related deaths and 3,000-5,000 lung cancer deaths due to environmental tobacco smoke exposure have been predicted to occur each year.

The AHA's Council on Cardiopulmonary and Critical Care has concluded that environmental tobacco smoke is a major preventable cause of cardiovascular disease and death. The council strongly supports efforts to eliminate all exposure of nonsmokers to environmental tobacco smoke. This requires that environmental tobacco smoke be treated as an environmental toxin, and ways to protect workers and the public from this health hazard should be developed. According to a 1989 Gallup survey commissioned by the American Lung Association, 86% of nonsmokers think that environmental tobacco smoke is harmful and 77% believe that smokers should abstain in the presence of nonsmokers. However, programs aimed at further educating the public about the cardiovascular effects on nonsmokers of exposure to environmental tobacco smoke must be strengthened and remain a major component of the AHA mission. A smoke-free environment in the home, public buildings, and workplace should be the goal of society.

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Appendix C

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THE HEALTH CONSEQUENCES OF INVOLUNTARY SMOKING

a report of the Surgeon General

1986



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
Center for Health Promotion and Education
Office on Smoking and Health
Rockville, Maryland 20857

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parents smoke, a stronger relationship exists than if only one parent smokes.

What future respiratory burden these findings may represent for these children later in life is not known. As a former pediatric surgeon, I strongly urge parents to refrain from smoking in the presence of children as a means of protecting not only their children's current health status but also their own.

Diseases Other Than Lung Cancer

Several studies have provided data on the relationship between ETS and cancers other than lung cancer and on ETS exposure and cardiovascular disease. However, further research in these areas will be required to determine whether an association exists between ETS exposure and an increased risk of developing these diseases.

Policies Restricting Smoking in Public Places

The growth in our understanding of the disease risk associated with involuntary smoking has been accompanied by a change in the social acceptability of smoking and by a growing body of legislation, regulation, and voluntary action that addresses where smoking may occur in public. Forty States and the District of Columbia now have some form of legislation controlling or restricting smoking in various public settings. Some States limit smoking to only a few designated areas; however, States are increasingly developing and implementing comprehensive legislation that restricts smoking in many public settings, including the workplace. Nine States have restrictions that cover smoking not only by public employees but also by employees in the private sector.

No systematic evaluation of the effects these measures may have on smoking behavior has been conducted, but there is little doubt that strong public sentiment exists for implementing such restrictions. A number of national surveys conducted by voluntary health organizations, government agencies, and even the tobacco industry have documented that an overwhelming majority of both smokers and nonsmokers support restricting smoking in public.

Public Health Policy and Involuntary Smoking

The 1986 Surgeon General's Report on the Health Consequences of Involuntary Smoking clearly documents that nonsmokers are placed at increased risk for developing disease as the result of exposure to environmental tobacco smoke.

Critics often express that more research is required, that certain studies are flawed, or that we should delay action until more conclusive proof is produced. As both a physician and a public health

Cigarette smoke is well established as a human carcinogen. The chemical composition of ETS is qualitatively similar to mainstream smoke and sidestream smoke and also acts as a carcinogen in bioassay systems. For many nonsmokers, the quantitative exposure to ETS is large enough to expect an increased risk of lung cancer to occur, and epidemiologic studies have demonstrated an increased lung cancer risk with involuntary smoking. In examining a low-dose exposure to a known carcinogen, it is rare to have such an abundance of evidence on which to make a judgment, and given this abundance of evidence, a clear judgment can now be made: exposure to ETS is a cause of lung cancer.

The data presented in this Report establish that a substantial number of the lung cancer deaths that occur among nonsmokers can be attributed to involuntary smoking. However, better data on the extent and variability of ETS exposure are needed to estimate the number of deaths with confidence.

Respiratory Disease

Acute and chronic respiratory diseases have also been linked to involuntary exposure to tobacco smoke; the evidence is strongest in infants. During the first 2 years of life, infants of parents who smoke are more likely than infants of nonsmoking parents to be hospitalized for bronchitis and pneumonia. Children whose parents smoke also develop respiratory symptoms more frequently, and they show small, but measurable, differences on tests of lung function when compared with children of nonsmoking parents.

Respiratory infections in young children represent a direct health burden for the children and their parents; moreover, these infections, and the reductions in pulmonary function found in the school-age children of smokers, may increase susceptibility to develop lung disease as an adult.

Several studies have reported small decrements in the average level of lung function in nonsmoking adults exposed to ETS. These differences may represent a response of the lung to chronic exposure to the irritants in ETS, but it seems unlikely that ETS exposure, by itself, is responsible for a substantial number of cases of clinically significant chronic obstructive lung disease. The small magnitude of the changes associated with ETS exposure suggests that only individuals with unusual susceptibility would be at risk of developing clinically evident disease from ETS exposure alone. However, ETS exposure may be a factor that contributes to the development of clinical disease in individuals with other causes of lung injury.

Cardiovascular Disease

A few studies have examined the relationship between involuntary smoking and cardiovascular disease, but no firm conclusion on

the relationship can be made owing to the limited number of deaths in the studies.

Irritation

Perhaps the most common effect of tobacco smoke exposure is tissue irritation. The eyes appear to be especially sensitive to irritation by ETS, but the nose, throat, and airway may also be affected by smoke exposure. Irritation has been demonstrated to occur at levels that are similar to those found in real-life situations. The level of irritation increases with an increasing concentration of smoke and duration of exposure. In addition, participants in surveys report irritation and annoyance due to smoke in the environment under real-life conditions.

Determinants of Exposure

Exposure to ETS has been documented to be common in the United States, but additional data on the extent and determinants of exposure are needed to identify individuals within the population who have the highest exposure and are at greatest risk. Studies with biological markers and measurements of ETS components in indoor air confirm that measurable exposure to ETS is widespread. However, within exposed populations, levels of cotinine excretion and presumably ETS exposure vary greatly.

In a room or other indoor area, the size of the space, the number of smokers, the amount of ventilation, and other factors determine the concentration of tobacco smoke in the air. The technology for the cost-effective filtration of tobacco smoke from the air is not currently available, and because of their small size, the smoke particles remain suspended in the air for long periods of time; thus, the only way to remove smoke from indoor air is to increase the exchange of indoor air with clean outdoor air. The number of air changes per hour required to maintain acceptable indoor air quality is much higher when smoking is allowed than when smoking is prohibited.

Environmental tobacco smoke originates at the lighted tip of the cigarette, and exposure to ETS is greatest in proximity to the smoker. However, the smoke rapidly disseminates throughout any airspace contiguous with the space in which the smoking is taking place. Dissemination of smoke is not uniform, and substantial gradients in ETS levels have been demonstrated in different parts of the same airspace. The time course of tobacco smoke dissemination is rapid enough to ensure the spread of smoke throughout an airspace within an 8-hour workday. In the home, the presence of even one smoker can significantly increase levels of respirable suspended particulates.

These data lead to the conclusion that the simple separation of smokers and nonsmokers within the same airspace will reduce, but

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for parental smoking and childhood cancer is also not clear, and evaluation of this association is made difficult by the various definitions of exposure that have been used, including maternal and paternal smoking before, during, and after the pregnancy. Mothers and fathers who smoke during a pregnancy generally smoked before the conception and continue to smoke after the pregnancy. Thus, an effect of involuntary smoking after birth cannot readily be distinguished from genetic or transplacentally mediated effects.

Cardiovascular Diseases

A causal association between active cigarette smoking and cardiovascular disease is well established (US DHHS 1983). The relationship between cardiovascular disease and involuntary smoking has been examined in one case-control study and three prospective studies. In the case-control study by Lee and colleagues (1986), described previously, ischemic heart disease cases and controls did not show a statistically significant difference in their exposure to involuntary smoking, based on the smoking habits of spouses or on an index accounting for exposure at home, at work, and during travel and leisure. In the Japanese cohort study, Hirayama (1984b, 1985) reported an elevated risk for ischemic heart disease ($N=494$) in nonsmoking women married to smokers. The standardized mortality ratios when the husbands were nonsmokers, ex-smokers or smokers of 19 or more cigarettes per day, and smokers of 20 or more cigarettes per day were 1.0, 1.10, and 1.31, respectively (one-sided p for trend, 0.019).

In the Scottish followup study (Gillis et al. 1984), nonsmokers not exposed to tobacco smoke were compared with nonsmokers exposed to tobacco smoke with respect to the prevalence of cardiovascular symptoms at entry and mortality due to coronary heart disease. There was no consistent pattern of differences in coronary heart disease or symptoms between nonsmoking men exposed to tobacco smoke and their nonexposed counterparts. Nonsmoking women exposed to tobacco smoke exhibited a higher prevalence of angina and major ECG abnormality at entry, and also a higher mortality rate for all coronary diseases. However, rates of myocardial infarction mortality were higher for exposed nonsmoking men and women compared with the nonexposed nonsmokers. The rates were 31 and 4 per 10,000, respectively, for the nonexposed nonsmoking men and women, and 45 and 12 per 10,000, respectively, for the exposed nonsmoking men and women. None of the differences were tested for statistical significance.

In the Japanese and the Scottish studies, other known risk factors for cardiovascular diseases, i.e., systolic blood pressure, plasma cholesterol, were not accounted for in the analysis.

In a study of heart disease, Garland and coworkers (1985) enrolled 82 percent of adults aged 50 to 79 between 1972 and 1974 in a predominantly white, upper-middle-class community in San Diego, California. Blood pressure and plasma cholesterol were measured at entry, and all participants responded to a standard interview that asked about smoking habits, history of heart disease, and other health-related variables. Excluding women who had a previous history of heart disease or stroke or who had ever smoked, 695 currently married nonsmoking women were classified by their husbands' self-reported smoking status at enrollment. After 10 years of followup, there were 19 deaths due to ischemic heart disease; the age-standardized mortality rates for nonsmoking wives whose husbands were nonsmokers, ex-smokers, and current smokers were 1.2, 3.6, and 2.7, respectively (one-sided p for trend, ≤ 0.10). After adjustment for age, systolic blood pressure, total plasma cholesterol, obesity index, and years of marriage, the relative risk for death due to ischemic heart disease for women married to current or former smokers at entry compared with women married to never smokers was 2.7 (one-sided $p \leq 0.10$).

The study's findings are not convincing from the point of view of sample stability. The total number of deaths due to ischemic heart disease was small, and the denominator in the relative risk calculation is unstable, based on the deaths of two women whose husbands had never smoked. Moreover, it is well established that the risk of coronary heart disease is substantially lower among those who have stopped smoking (US DHHS 1983), although the amount of time required for this change after cessation of smoking is not clear (Kannel 1981). In this study, 15 of 19 deaths occurred in nonsmoking women married to husbands who had stopped smoking at entry, and the age-standardized rate for ischemic heart disease was highest in this group. The high proportion of deaths in nonsmoking women married to men who became ex-smokers implies that the excess resulted from a sustained effect of involuntary smoking. More detailed characterizations of exposure to ETS and specific types of cardiovascular disease associated with this exposure are needed before an effect of involuntary smoking on the etiology of cardiovascular disease can be established.

One study (Aronow 1978a,b) suggested that involuntary smoking aggravates angina pectoris. This study was criticized because the end point, angina, was based on subjective evaluation, and because other factors such as stress were not controlled for (Coodley 1978; Robinson 1978; Waite 1978; Wakehan 1978). More important, the validity of Aronow's work has been questioned (Budiansky 1983).

Conclusions

1. Involuntary smoking can cause lung cancer in nonsmokers.
2. Although a substantial number of the lung cancers that occur in nonsmokers can be attributed to involuntary smoking, more data on the dose and distribution of ETS exposure in the population are needed in order to accurately estimate the magnitude of risk in the U.S. population.
3. The children of parents who smoke have an increased frequency of hospitalization for bronchitis and pneumonia during the first year of life when compared with the children of nonsmokers.
4. The children of parents who smoke have an increased frequency of a variety of acute respiratory illnesses and infections, including chest illnesses before 2 years of age and physician-diagnosed bronchitis, tracheitis, and laryngitis, when compared with the children of nonsmokers.
5. Chronic cough and phlegm are more frequent in children whose parents smoke compared with children of nonsmokers. The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study.
6. The children of parents who smoke have small differences in tests of pulmonary function when compared with the children of nonsmokers. Although this decrement is insufficient to cause symptoms, the possibility that it may increase susceptibility to chronic obstructive pulmonary disease with exposure to other agents in adult life, e.g., active smoking or occupational exposures, needs investigation.
7. Healthy adults exposed to environmental tobacco smoke may have small changes on pulmonary function testing, but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to environmental tobacco smoke alone.
8. A number of studies report that chronic middle ear effusions are more common in young children whose parents smoke than in children of nonsmoking parents.
9. Validated questionnaires are needed for the assessment of recent and remote exposure to environmental tobacco smoke in the home, workplace, and other environments.
10. The associations between cancers, other than cancer of the lung, and involuntary smoking require further investigation before a determination can be made about the relationship of involuntary smoking to these cancers.
11. Further studies on the relationship between involuntary smoking and cardiovascular disease are needed in order to

determine whether involuntary smoking increases the risk of cardiovascular disease.

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ENVIRONMENTAL TOBACCO SMOKE

Measuring Exposures and Assessing Health Effects

Committee on Passive Smoking
Board on Environmental Studies and Toxicology
National Research Council

Chapter 14
"Cardiovascular system"

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Cardiovascular System

The effects of active smoking on exercise tolerance, blood pressure, and the risk of developing cardiovascular disease have been reviewed elsewhere (U.S. Public Health Service, 1983). This chapter discusses studies of ETS exposure to nonsmokers and subsequent possible cardiovascular effects. The constituents that are thought to have the greatest effect on the cardiovascular system are carbon monoxide (CO) and nicotine. The possibility exists that the mechanisms, as well as the magnitude of the effects, for acute and chronic cardiovascular effects may be different for exposure to whole smoke and to ETS.

ACUTE CARDIOVASCULAR EFFECTS OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE

Administration of nicotine at level similar to those induced by active cigarette smoking is shortly followed by increases in heart rate and blood pressure (U.S. Public Health Service, 1983). Platelet aggregation has been shown to be increased in in vitro studies. CO rapidly combines with hemoglobin in the blood to form carboxyhemoglobin (COHb), thereby leading to some degree of tissue hypoxia. CO combines with muscle myoglobin, which is followed by some muscle hypoxia. The level of exposure of the nonsmoker to these cigarette smoke constituents, however, is less than that of the active smoker, and the effects are expected to be less.

Table 14-1 reviews some of the increases in COHb levels as seen in both experimental and observational studies. The levels of

TABLE 14-1 Carbon Monoxide and Carboxyhemoglobin Levels in Nonsmoking Individuals

Experimental Studies (Controlled Chambers)

Study	No. of Cigarettes/h/10 m ³	No. of Subjects	CO, ppm ^a	Carboxyhemoglobin	
				Control	Change
Anderson and Dalhamm, 1973	3:1	—	4.5	0.3	0
Dahms et al., 1981	—	10	15-20	0.6	+0.4
Harke, 1970	3.9	7	30	0.9	+1.2
Huch et al., 1980	2.3	12	—	1.3	+0.5
Hugod et al., 1978	2.5	10	20	0.7	+0.9
Pimm et al., 1978	2.4	10	24	0.5	+0.3
	2.4	10	24	0.7	+0.2
Polak, 1977	6.7	15	23	2.0	+0.3
Russell et al., 1973	15.1	12	38	1.6	+1.0
Seppänen and Uusitalo, 1977	3.8	28	16	1.6	+0.4
Srch, 1967	50	—	90	2	+3

Observational Studies

Study	Subjects/Exposure	No. of Subjects	Nonexposed: Exposed	
			Carboxy-hemoglobin, %	CO Ex-pired, ppm
Folliart et al., 1982	Flight attendants/8 h	6	1.0:0.7	
Jarvis et al., 1983	Normal/public house for 2 h	7		4.7:10.6
Lightfoot, 1972	Normal/submarine		—:1.0	
Wald et al., 1981	Participants in health screening program	6,641		
Jarvis et al., 1984	Normal/self report	10	0.9:0.8	5.7:5.5
Seppänen and Uusitalo, 1977	Restaurant for 5 h (CO:2.5-15 ppm)	47	2.1:2.1	
	Office for 8 h (CO:2.5 ppm)	15	2.3:2.3	

^aCarbon monoxide (CO) measured as a proxy to indicate the concentration of ETS in the chamber.

COHb commonly observed in active smokers are higher, ranging between 4 to 6 percent, rarely greater than 12 percent (Schievelbein and Richter, 1984). Because exposure of the nonsmoker is qualitatively different than exposure to smokers, a simple scaling down of effects observed in active smokers does not appear to be fully appropriate. Therefore, the effects of exposure to nicotine,

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TABLE 14-2 Resting Acute Cardiovascular Effects in Nondiseased Humans of Exposure to Environmental Tobacco Smoke

Authors	Study Population	Conditions	Results		
			Measured Variable	Before	After
Luguet et al., 1970	40 children	Room: 9 m ³	Heart rate	89	97
		No. cig.: 6	Blood pressure	116/67	120/72
		Time: 15 min			
Harke and Bleichert, 1972	10	Room: n.g.	Heart rate	72 ± 8	74 ± 12
		No. cig.: 150	Blood pressure	123/84	121/84
		Time: 20 min	Skin temperature		
			(-°C/min)	0	0.0273
Rummel et al., 1975	56	Room: 30 m ³	Heart rate	72 ± 10	71 ± 11
		No. cig.: 6-8	Blood pressure	117/71	117/71
		Time: 20 min			
Hurshman et al., 1978	8	Room: n.g.	Heart rate	73	79
		No. cig.: 2-6	Blood pressure	107/67	114/68
		Time: 10 min			
Pimm et al., 1978	10 males	Room: 14.6 m ³	Heart rate	84(F)	80(F)
	10 females	No. cig.: 7		77(M)	70(M)
	Age = 22.3	Time: 2 h			

CO, or ETS need to be separately studied. In addition, consideration needs to be given to persons of different sensitivity or vulnerability.

Healthy Subjects

Table 14-2 lists studies that report on the consequences of exposure of nondiseased individuals to ETS for periods up to 2 hours under experimental, resting conditions. There were no significant changes noted in heart rate or blood pressure in school-aged children or in adult men and women.

Two studies evaluated the physiologic responses to exercise with and without exposure to ETS. In the first, Pimm et al. (1978) (see also Table 14-2) had subjects perform a 7-minute progressive exercise test on an electronic bicycle ergometer. During exercise, the women had higher heart rates after exposure to ETS when compared with control conditions (differences of 6.3 beats per minute at 2 minutes and 4.5 beats per minute at 7 minutes, $p < 0.01$). The recovery heart rates were not significantly different. The men, however, showed little difference between test and

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control conditions (differences of -0.1 beats per minute at 2 minutes and 1.5 beats per minute at 7 minutes). In the second study, Sheppard and colleagues (1979b) tested 11 males and 12 females at two different levels of ETS (i.e., 7 cigarettes over 2 hours, CO = 20 ppm, or 9 cigarettes over 2 hours, CO = 31 ppm). Under both exposure conditions, contrary to expectations, both the increment in heart rate and average heart rate were less with ETS exposure.

In summary, for normal young adult males and females, no significant acute effects of ETS exposure on heart rate or blood pressure have been reported, either under resting or aerobic conditions.

There have been several studies of exposure of normal subjects under resting and aerobic conditions to low levels of CO but higher than those found with ETS exposure (reviewed in Environmental Protection Agency, 1984). No significant effects were found in healthy, exercising subjects during short-term exposure (e.g., Drinkwater et al., 1974; Raven et al., 1974a,b; DeLucia et al., 1983).

Angina Patients

Angina pectoris is a symptom complex involving feelings of pressure and pain in the chest, which is produced by mild exercise or excitement, presumably because of insufficient oxygen supply to the heart muscle. Under conditions of ETS exposure, the CO levels are increased, thus possibly placing individuals with angina at an increased risk of recurrent episodes.

Anderson et al. (1973) and Aronow and his colleagues, in a series of experiments (1973, 1974, 1978, 1981) (Table 14-3), studied angina patients under aerobic conditions with exposures to low levels of CO and to ETS. Ten patients with diagnosed angina pectoris, of whom two were smokers and eight exsmokers, were tested (Aronow et al., 1978). Significant increases in systolic blood pressure and heart rate, and decreases in time to onset of angina, were noted when the subjects were exposed to smoke in either ventilated or unventilated rooms (the actual levels of CO under these conditions were not noted). There were some subjective elements in the evaluation of these patients, and the physician conducting these tests was aware of the test conditions, i.e., smoking or not and ventilated or not. Consequently, the findings of this study, in

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TABLE 14-3 Acute Cardiovascular Effects of Exposure to CO or Environmental Tobacco Smoke by Nonsmoking Angina Patients

Study	Design	No.	Conditions	Results
Anderson et al., 1973	Double-blind, Cross-over	10 ^a	CO: 50 ppm or 100 ppm Time: 4 h for 5 days	Mean duration before onset of pain shortened (50 ppm and 100 ppm); duration of pain longer (100 ppm only).
Aronow and Isbell, 1973	Double blind, Cross-over	10 ^b	CO: 50 ppm Time: 2 h	Times until onset decreased; decrease in BP and heart rate at angina
Aronow, 1978	Not blinded	10 ^c	No. cig.: 15 Time: 2 h Room: 30.28 m ³	Earlier onset of angina; increased systolic BP and heart rate at angina
Aronow et al., 1979	Double-blind, Cross-over	20	COHb: 4%	Impairment in visualization test
Aronow, 1981	Double-blind, Cross-over	15	CO: 50 ppm Time: 1 h COHb: 2%	Time until onset decreased; decreased systolic BP and heart rate at angina

^aIncludes five smokers and five nonsmokers.^bNot current smokers.^cIncludes eight exsmokers and two current smokers.

the absence of a true double-blind approach, require verification by other research workers.

The effects of rapid angina onset would be expected to be due to increased COHb levels. Anderson et al. (1973) and Aronow et al. (1973, 1981) exposed angina patients to low levels of CO. In these studies, angina pain appeared when COHb levels of patients were measured at 2 and 4%. These studies have been reviewed extensively as part of the Environmental Protection Agency's (1984) activity in establishing air quality criteria for carbon monoxide. The review group found that the results were suggestive for effects at COHb levels above 3%, based on animal and theoretical models. There is concern that elevated levels of CO exposure may affect the electrical stability of the heart in previously compromised heart muscle, thus possibly leading to sudden death. The levels reviewed in Table 14-1 are close to the 3% level. This suggests that there is reason to be concerned with possible effects of exposure. However, a firm quantitative estimate of the risk to nonsmoking persons, under conditions of ETS exposure, cannot be made from the literature at this time.

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CARDIOVASCULAR DISEASE MORBIDITY AND MORTALITY

Possible pathophysiologic mechanisms for the atherogenic influence of cigarette smoking were reviewed in the 1983 Report of the Surgeon General. Experimental studies of subcutaneous or intravenous administration of nicotine in rabbits (Schievelbein et al., 1970; Schievelbein and Richter, 1984) and monkeys (Liu et al., 1979) have demonstrated that long-term exposure leads to arteriosclerotic lesions. Exposure to carbon monoxide also leads to atherosclerosis in rabbits, pigeons, and other animals (Astrup and Kjeldsen, 1979). Studies of whole tobacco smoke indicate that total serum cholesterol concentrations are increased and the ratios of the various lipoprotein fractions are changed (McGill, 1979). The contribution of whole tobacco smoke to modifying the lipoprotein fractions is not conclusive. However, there have not been experimental studies of the effects of ETS exposure or administration of ETS extracts.

Smoking and Cardiovascular Disease

The effects of active smoking on human health are summarized in the Surgeon General's report *The Health Consequences of Smoking: Cardiovascular Disease* (U.S. Public Health Service, 1983). The principal conclusions are that cigarette smokers experience a 70% greater coronary heart disease (CHD) death rate than do nonsmokers and that smokers of more than two packs per day have 2 to 3 times greater CHD death rates than nonsmokers. The incidence of CHD in smokers is twice that of nonsmokers. Heavy smokers (more than two packs per day) have an almost fourfold increase. The relative risk in smokers for sudden death is greater than that for all deaths from CHD. The relative risk in young smokers is greater than that in older smokers. The relative risk for young women smokers, especially those who use oral contraceptives, is greater than 5.

The excess relative risk associated with smoking declines rapidly upon cessation of smoking, in some studies as much as 50% in 1 year. For exsmokers who previously smoked more than one pack per day, the residual excess risk also declines, but never completely disappears. The decline in risk on cessation of smoking cannot be explained by differences in known cardiac risk factors

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between individuals who continue smoking and individuals who have quit. Smokers who have used only pipes or cigars did not appear to experience a substantially greater CHD risk than non-smokers.

The rapid decline in risk associated with smoking cessation and the greater relative risk for sudden death suggest that active smoking can precipitate cardiac events in individuals with preexisting coronary artery disease. Autopsy evidence of increased arteriosclerosis in smokers, coupled with the fact that risk of exsmokers never returns to the levels found in nonsmokers, suggests that cigarette smoking is also implicated in the development of arteriosclerotic cardiovascular disease (ASCVD). The mechanism by which cigarette smoke may lead to the development of chronic ASCVD, sudden death, or acute myocardial infarction is unknown. There appears, however, to be no threshold in the number of cigarettes smoked below which there is no increase in risk.

Data on uptake of cotinine by nonsmokers exposed to ETS indicate that the exposure in nonsmokers chronically exposed to ETS is approximately 1% that of an active smoker (who smokes one pack per day) (see Chapters 8 and 12). If the excess relative risk for CHD mortality or morbidity is a linear, nonthreshold function of dose and, further, if the excess risk of CHD in a one-pack-a-day smoker is twofold, then the relative risk from CHD in nonsmokers exposed to ETS (compared to true nonsmokers) would be approximately 1.02. Such relative risks would be difficult to detect or estimate reliably in nonexperimental studies. Such small increases in relative risk are of the same order of magnitude as what might arise from expected residual confounding due to unmeasured covariates. Nonetheless, because of the large number of cardiovascular deaths each year, these possibilities deserve close attention and further study that could lead to firmer estimates of excess risk.

Studies of Environmental Tobacco Smoke Exposure and Mortality from Cardiovascular Disease

Garland et al. (1985) have reported that, in a prospective study of the effect of passive smoking, the age-adjusted rates of cardiac disease deaths in nonsmoking women whose husbands were former or current smokers were significantly elevated. It is

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not certain, however, that the report is correct, because of a possible miscalculation or misuse of the Mantel-Haenszel statistic and some other methodologic problems. Data for the wives of former smokers were grouped with wives of current smokers. If this grouping were made after examining the data, which indicated that the risk was greater among the women whose husbands were former smokers, then this combination would be suspect. The p values based on the Mantel-Haenszel test may be inappropriate in view of the small sample sizes. The authors employ the Cox Proportional Hazard analysis to control for other factors associated with cardiovascular risk, such as age, blood pressure, cholesterol, obesity, years of marriage, etc. They report a relative risk for women married to current or former smokers compared with women married to never-smokers of 2.7 (Garland, 1985, corrected from an earlier report). The p value (< 0.10) associated with this estimate is based on the asymptotic assumptions that are implicit in likelihood-based inference from the Cox model. These assumptions may not hold for small sample sizes. In summary, because of the small sample sizes, the significance calculations arising from this study must be looked upon as approximations.

Gillis et al. (1984) reported the results of a follow-up study of residents of two urban communities in Scotland. Nonsmokers exposed to cigarette smoke in their homes had a slightly higher rate of myocardial infarction than those unexposed. The sample size was small, so that few of the results were statistically significant, and other risk factors for myocardial infarction were not controlled for.

Hirayama (1984) reported the results of a 15-year prospective study of nonsmoking Japanese women classified at start of follow-up by the smoking status of their husbands. A relative risk from ischemic heart disease of 1.3 was found for nonsmoking women whose husbands smoked more than 19 cigarettes per day compared with nonsmoking women whose husbands did not smoke. A Mantel-Haenszel test for a linear trend was significant at the $p < 0.01$ level.

It is unlikely that Hirayama's results can be explained by chance. The potential biases inherent in this study (see Chapter 12) limit the weight that can be placed on these results. The observed relative risk of 1.3 is at the upper limit of the expectations derived from extrapolations from active smokers, unless the uptake of the active component of cigarette smoke to which

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passive smokers are exposed is of the order of 10% of that of active smokers. Matsukura et al. (1984) have suggested that such high levels of uptake in passive smokers may be seen in Japan. If there were independent evidence that nonsmokers exposed to other people's cigarette smoke do not differ on known risk factors for CHD from unexposed nonsmokers, more reliance could be placed on Hirayama's results.

Svensden et al. (1985) reported on the effect of cigarette smoke exposure to smoking wives among men participating in the Multiple Risk Factor Intervention Trial (MRFIT). MRFIT, which began in the mid-1970s, was a randomized primary prevention trial designed to test the effect of a multifactor intervention program on mortality from coronary heart disease in men with previous cardiac episodes. The men were chosen for participation if they had at least two of three risk factors for heart disease, including smoking, high cholesterol levels, or high blood pressure. The results reported by Svendsen et al. (1985), based on the group of men who never smoked but whose wives may or may not have been smokers, indicate no difference between exposed (i.e., smoking wives) and nonexposed (i.e., nonsmoking wives) of nonsmoking men for blood pressure or serum cholesterol. The MRFIT study demonstrates a roughly twofold increase in the risk of CHD mortality and morbidity among nonsmokers exposed to ETS. The sample size was small, and the results were not statistically significant. Adjustment for other risk factors for CHD did not change the estimates of effect.

SUMMARY AND RECOMMENDATIONS

What Is Known

1. No statistically significant effects of ETS exposure on heart rate or blood pressure were found in healthy men, women, and school-aged children during resting conditions. During exercise there is no difference in the cardiovascular changes for men and women between conditions of exposure to ETS and control conditions.
2. With respect to chronic cardiovascular morbidity and mortality, although biologically plausible, there is no evidence of statistically significant effects due to ETS exposure, apart from the study by Hirayama in Japan.

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What Scientific Information Is Missing

1. Experimental studies with animal models need to be performed with ETS to determine whether the cardiovascular changes seen following exposure to whole smoke also occur following exposure to ETS.

2. Existing studies have not provided evidence of serious harm in people with heart disease. With regard to angina onset, the findings are uncertain and need to be repeated.

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Environmental Tobacco Smoke

*Proceedings of the International
Symposium at McGill University
1989*

Waxler, L. M.

Chapter 8 "Environmental Tobacco
Smoke and Cardiovascular Disease:
A Critique of the Epidemiological
Literature and Recommendations for
Future Research" pp. 139-152

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Joseph M. Wu
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Environmental Tobacco Smoke and Cardiovascular Disease: A Critique of the Epidemiological Literature and Recommendations for Future Research

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This paper evaluates the current epidemiological literature examining the possible relationship between exposure to environmental tobacco smoke ("ETS") and cardiovascular disease. Based on the available evidence, it is this author's opinion that it has not been demonstrated that exposure to ETS increases the risk of cardiovascular disease. This paper evaluates seven studies that examine this issue (table 8-1). Five of the studies are prospective in nature, one is a case-control design (retrospective), and one is an experimental design examining the biological plausibility of a link between ETS and cardiovascular disease.

Several key points of epidemiology need to be mentioned here, and should be kept in mind when reading the critiques of the seven studies. To prove causality five criteria need to be met. The first relates to the strength of the association. There are three elements to this criterion. First, there must be a statistically significant increase in the incidence of the disease in the exposed population compared with the non-exposed population. Second, for the association to be regarded as meaningful, a relative risk of 2.0 or greater is generally considered necessary. Third, the association should also be dose dependent, i.e., higher doses are associated with higher incidence of disease.

The second point is that consistency of the association must exist among the relevant studies. This means that similar rates of disease must occur at different times and places, under comparable study designs.

A third point deals with the temporal aspect of the association. This means that exposure to ETS should have occurred at a reasonable time before the onset of disease, given what is known about how long it takes for cardiovascular disease to develop.

A fourth point is specificity of the association. With ETS, this means that exposure to ETS must be shown to be associated with cardiovascular disease while controlling for all confounding variables.

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Table 8-1
Environmental Tobacco Smoke and Cardiovascular Disease

	Design	Findings	Methodological Problems
1. Hirayama (1981, 1984)	Sixteen year prospective study of nonsmoking Japanese women classified at start of follow-up by the smoking status of their husbands. 142,857 women 40 and over (91,540 nonsmoking wives).	<ol style="list-style-type: none"> 1. Relative risk of 1.31 for ischemic heart disease for nonsmoking women whose husbands smoked > 19 cigarettes per day compared with nonsmoking women whose husbands did not smoke. 2. Mantel-Haenszel significant at $p < .019$, 1984. 3. "Passive smoking did not seem to increase the risk of developing . . . ischemic heart disease." —Hirayama, 1981. 	<ol style="list-style-type: none"> 1. Potential biases. 2. Misclassification of smokers and non-smokers. 3. Misclassification of dose response (number of cigarettes smoked per day). 4. Looked at spouse exposure only, not workplace. 5. No control for indoor air pollution, e.g., cooking with kerosene stoves. 6. Not representative of Japanese population—only agriculture represented. 7. Non-random sample of prefectures—only a convenience sample.
2. Garland (1985)	Prospective—enrolled 82% of adults ages 50–79 between 1972–1974 in a community in San Diego. Blood pressure and plasma cholesterol measured at entry; interviewed all cohort of 695 current married non-smoking women free of heart disease; ten year follow-up.	<ol style="list-style-type: none"> 1. Elevated cardiac disease deaths in non-smoking women, ages 50–79, whose husbands were former or current smokers. 2. 19 deaths from ischemic heart disease after ten years. 	<ol style="list-style-type: none"> 1. Some misgrouping—wives of former smoker were grouped with wives of current smokers. 2. Small sample sizes, value may be inappropriate based on Mantel-Haenszel, and may only be an approximation; still p was only $p < .10$. 3. 15 of 19 deaths occurred in nonsmoking women married to former smokers—puzzling results.
3. Gillis (1989)	Two urban communities in Scotland. Ten year follow-up report. 8,128 adults ages 45–64.	Non-smokers exposed to cigarette smoke in their homes had a slightly higher rate of myocardial infarction than those unexposed.	<ol style="list-style-type: none"> 1. Small sample size. 2. Few of the results were statistically significant.

Table 8

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Table 8-1 continued

Methodological Problems	Design	Findings	Methodological Problems
biases. location of and non- location of inse (cigarettes or day). spouse only, not for pollution, ing with caves. tentative of —only d. om sample res—only nce rouping— rmer re ith wives smokers. le sizes, be ate based Haenszel, nly be an rion; still p < .10. aths g women former puzzling le size. results tically	<p>4. Svendsen (1987)</p> <ol style="list-style-type: none"> 1. Multiple Risk Factor Intervention Trial (MRFIT). 2. Randomized primary prevention trial designed to test the effect of a multifactor intervention program on mortality from coronary heart disease in men with previous cardiac episodes. 3. Men were chosen for participation if they had at least two of three risk factors for heart disease (smoking, high cholesterol levels, high blood pressure). <p>5. Helsing (1988)</p> <ol style="list-style-type: none"> 1. Twelve year study, executed in Washington County, Maryland. 2. July, 1963 census of 91,909 people. 3. Whites only. 4. Death certificates collected from July, 1963 through July, 1975. 5. Non-smokers, ages 25 and over. 6. 4,162 men and 14,873 women. 	<ol style="list-style-type: none"> 1. No difference between smoking wives and nonsmoking wives for non-smoking men for blood pressure or cholesterol. 2. Roughly two-fold increase in risk of CHD mortality and morbidity among nonsmoking men exposed to ETS of wives. <ol style="list-style-type: none"> 1. Death rates from arteriosclerotic heart disease were higher among men (Relative risk = 1.31) and women (relative risk = 1.24) who lived with smokers in 1963, after adjustment for age, marital status, years of schooling, and quality of housing index. 2. For women, relative risk increased significantly ($p < .005$) for dose response (increasing levels of exposure). 3. Men—little evidence of a dose response relationship. 	<ol style="list-style-type: none"> 1. Sample size small. 2. Results—not statistically significant. <ol style="list-style-type: none"> 1. Only smoking data collected on every person was in 1963. 2. No measurement of changes in smoking habits. 3. No data on household changes from 1963–1975. 4. Very little other risk factor data for heart disease. 5. No diet, exercise, blood pressure, cholesterol data, or ETS exposure out of home.

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Table 8-1 continued

	Design	Findings	Methodological Problems
6. Lee (1986)	Case-control	Ischemic heart disease cases and controls did not show a statistically significant difference in their exposure to involuntary smoking, based on smoking habits of spouses or on an index accounting for exposure at home, at work, and during travel and leisure.	Case-control methodological issues.
7. Aronow (1978)	Experimental design.	ETS aggravates angina pectoris.	1. Endpoint of angina based on subjective evaluation. 2. Stress not controlled for.

The fifth point is that there must be biological plausibility. This means that under experimental conditions exposure to the pertinent substance (or similar substances) must be shown to cause biological changes that can lead to the disease in question.

All five conditions must be met for causality to be established. We will return to these points at the end of the paper, when we examine recommendations for future research.

I. Summary of Epidemiological Literature

A. Prospective Studies

1. **Hirayama.** Hirayama (1984) conducted a prospective cohort study in 29 health center districts in six prefectures in Japan between January 1966 and December 1981. In total, 265,118 adults (122,261 men and 142,857 women) aged 40 years and over were followed. Ninety-five percent of the census population was interviewed between October and December 1965. Also, Hirayama established a record linkage system under which he gathered and analyzed death certificates, risk factor records, and a residence list obtained by an annual census. Questions on smoking habits were asked independently of husbands and wives at the beginning of the study. There were 91,540 non-smoking married women whose husbands' smoking habits were reported by questionnaire.

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In 1981, Hirayama (1981) concluded that "husbands' smoking habits seemed to have no effect on their non-smoking wives' risk of developing ischemic heart disease." Hirayama reported age/occupation standardized risk ratios for ischemic heart disease in non-smoking women by smoking habit of husband. When the husband was a non-smoker, the relative risk was 1.0. When the husband was an ex-smoker or smoked 1-19 cigarettes per day, the relative risk was .97. When the husband smoked 20 or more cigarettes/day, the relative risk was 1.03, and the reported p value was not significant at 0.393.

Hirayama (1984), in a 1984 paper, reported an elevated risk of ischemic heart disease morbidity based on further analyses. The relative risk for non-smoking married women for husbands who were non-smokers was 1.0; for husbands who were ex-smokers or smoked 1-19 cigarettes/day the relative risk was 1.10; and for husbands who smoked 20 or more cigarettes per day, the relative risk was 1.31, with a 90% confidence interval of 1.06 to 1.63. The reported p value was significant at .019.

Hirayama's study has several major methodological problems. The first problem is potential misclassification of smokers and non-smokers. Many of the wives who stated they were non-smokers may in fact be ex-smokers or even current smokers, and thus likely to have had or continue to have direct (as opposed to indirect) exposure to cigarette smoke.

The second problem is that Hirayama's study included a disproportionate number of women of lower socioeconomic status. In Japan, these women live in much closer proximity to their cooking quarters and may have more exposure to charcoal or kerosene stoves than women of higher socioeconomic status. This exposure has been associated with lung cancer in women in Hong Kong. Women in Japan of a higher socioeconomic status live farther away from their kitchens and are more likely to use electric burners. The Hirayama study failed to control for these confounding variables, which may be associated with ischemic heart disease.

A third problem is the misclassification of dose response. Ex-smoking husbands were lumped with current cigarette smokers of 1-19 cigarettes/day. Because ex-smokers are very different in their cigarette exposure rates and lifestyles than smokers of 1-19 cigarettes/day, this could skew the data.

A fourth problem is that Hirayama only examined the exposure of the wife in the context of the husband's cigarette smoking behavior. No attempt was made to quantify any exposure to ETS outside of the home, such as in the workplace.

A fifth problem is that the Hirayama study was not representative of Japanese society but only of an agriculturally based population, which is not typical for Japan. In addition, six prefectures were chosen to participate in the study based on the fact that they appear to have had the best conditions for collecting data. Hence, random sampling was not used.

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A sixth problem is that the Hirayama study did not control for other risk factors associated with cardiovascular disease, i.e., systolic blood pressure and plasma cholesterol.

Although the Hirayama study offers a large prospective cohort to examine the relationship between presumed exposure to environmental tobacco smoke and ischemic heart disease, one can not draw definitive conclusions because of the aforementioned methodological problems.

2. **Garland.** Garland (1985) conducted a prospective cohort study commencing in 1972–1974 in Rancho Bernardo, a white middle-class suburb of San Diego, California. The entire adult population was invited to participate, of which 82% agreed. The authors report that the respondents were representative of the total population with regard to age and sex.

All respondents were administered a standardized inventory, including questions about age, cigarette smoking, history of past hospitalizations for heart attack, heart failure or stroke, and number of years married. Cigarette smoking was assessed as current, former or never. Only current smokers were asked the number of cigarettes they smoked per day. No data were obtained for duration of smoking. In addition, blood pressure and plasma cholesterol were obtained.

An annual mailing was utilized to determine vital status for the next ten years. Death certificates were obtained for all decedents. Diagnosis of ischemic heart disease was validated by interviews with family and physicians, and/or examination of hospital records, for 85% of the deceased group.

Six hundred ninety-five (695) currently married nonsmoking women, ages 50–79, with no previous history of heart disease or stroke were followed based on their husband's self-reported smoking status in 1972–1974.

The results, after adjusting for age, systolic blood pressure, total plasma cholesterol, obesity index and years of marriage gave a relative risk of 14.9 of deaths from ischemic heart disease for women married to current or former smokers at entry compared with women married to never smokers. The *p* value was not significant, $p \leq .10$.

Important methodological problems exist with the Garland study. The first is that Garland later reported a corrected relative risk of 2.7 (not 14.9 as reported in the 1985 publication). The *p* value is still $< .10$ and not significant.

The second problem is that after ten years of follow-up, only 19 deaths from ischemic heart disease occurred. This small sample size is compounded by the fact that 15 of the 19 deaths occurred in nonsmoking women married to husbands who had stopped smoking at entry. Without more detailed characterization of these women's exposure to ETS, it is difficult to show an association between ETS and ischemic heart disease. As the study did not ascertain number of cigarettes smoked per day in former smokers, it is not

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possible to measure any sustained effects of ETS in this former smoking group.

Another methodological problem is that wives of former smokers were grouped with wives of current smokers, and it is difficult to determine the exact effect of ETS for this former smoking group.

Although the Garland study does make an attempt in a prospective cohort study to measure the effects of possible exposure to ETS on ischemic heart disease, and does control for important cardiovascular confounders, such as obesity, blood pressure and cholesterol, the small sample size and the lack of adequate measurement of ETS in a former cigarette smoking group make the results only suggestive and certainly not definitive.

3. **Gillis.** The Gillis study (1989) consists of a prospective cohort comprised of men and women aged 45–64 years who resided in two towns, Renfrew and Paisley, in the west of Scotland, between 1972 and 1976. Residents (15,399) of these two towns who met the age and residency criteria (an 80% response) agreed to participate; 7,997 were subjected to a cardiorespiratory screening examination, a self-administered questionnaire that included questions on smoking behavior. The eventual sample was comprised of 3,960 men and 4,037 women where it was possible to study varying exposures to tobacco smoke by cohabitants. Four groups were established for analysis purposes:

1. Control—neither the case nor anyone living at the same address had ever smoked.
2. Presumed ETS exposure in the home—the case had never smoked but lived at the same address as a subject who had smoked.
3. Single smoking—the case was a smoker or an ex-smoker and lived at the same address as a person who had never smoked.
4. Double smoking: the case was a smoker or an ex-smoker who lived at the same address as a subject who was also a smoker or ex-smoker.

Mortality was used as an endpoint and was obtained from the National Health Service. Cardiovascular signs and symptoms were also noted. Data presented were complete through December 1985, for an average follow-up of 11.5 years.

The authors present relative risks and 95% confidence intervals adjusted for age, sex, social class, diastolic blood pressure, serum cholesterol concentration and body mass index. Total mortality for ischemic heart disease was higher among those reportedly exposed to ETS in the home than controls.

Women with ETS exposure in the home were broken into two dose response categories for further analyses. These included: (1) the high exposure

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group, where the woman's cohabitee smoked 15 or more cigarettes daily, and (2) the low exposure group where the women's cohabitee smoked less than 15 cigarettes daily. Age-adjusted mortality from ischemic heart disease was higher for those in the high exposure category than in the low exposure group.

Relative risk was adjusted for age, sex, social class and cardiovascular variables including diastolic blood pressure, serum cholesterol concentrations and body mass index. Compared with controls, the relative risk was 2.01 for ischemic heart disease and was not significant.

The Gillis paper has several methodological problems. The first is that it does not have sufficient power to demonstrate an association between ETS and ischemic heart disease. The sample size is too small.

A second problem is that the relative risk of 2.01 for ischemic heart disease for non-smokers compared with controls is too similar to the relative risk of 2.27 for active smokers compared with controls to make sense. An explanation for this is not clear, but may be due to small sample size as well.

Potential biases also exist in the Gillis study. One potential bias is that those exposed to ETS within the home may have had higher exposures to ETS outside of the home compared with controls. A second potential bias is misclassification of women as non-smokers when they may be former smokers or current smokers.

Although the Gillis study suggests an association between ETS and cardiovascular mortality in non-smokers, the data lacks any statistical significance. Also, the study reports some confusing and similar relative risks for active and passive smokers, and is confounded by several important methodological biases. This study should be replicated in a much larger study population, with adequate statistical power.

4. Svendsen. Svendsen (1987) reports the results of the Multiple Risk Factor Intervention Trial (MRFIT), conducted from 1973–1982. The trial consisted of men, aged 35–57, recruited from 18 cities in the United States. Males who fell within the upper 10–15% risk score distribution for heart disease, based on an index comprised of serum cholesterol concentration, cigarette smoking and diastolic blood pressure, and free of overt coronary heart disease were randomized to one of two groups: (1) special intervention or (2) usual care. Participants in both groups were seen annually over six to eight years for risk factor measurement and a medical examination. A detailed smoking history was obtained at baseline and at all subsequent annual visits. Cause of death was evaluated by a committee of three cardiologists after examination of death certificates and other medical records.

Fourteen hundred of 12,866 men reported that they had never smoked at entry into the study. Of these 1400, 1,245 were married. Of the later group, 286 were married to women who smoked and 959 were married to women who did not smoke.

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The results compared ETS exposed husbands and non-ETS exposed husbands, where the husbands had *never* smoked. None of the endpoints showed statistical significance between the two groups, before or after adjustment for several variables, including age, baseline blood pressure, cholesterol, weight, alcohol consumption and education.

However, within the exposed group, increasing levels of cigarettes smoked daily by the wife had a statistically significant dose response relationship with husbands' CHD deaths. This is technically significant ($p = 0.04$) but is based on only one death in the 1-19 cigarettes smoked/day category.

A second analysis lumped never smoking husbands with ex-smoking husbands, calling these *non-smoking* husbands. This group was then evaluated on the basis of the smoking status of the wife. Non-smoking husbands of smokers did not show a statistically significant result when compared with husbands of non-smoking wives for mortality from CHD ($p = 0.15$) or from CHD itself as an endpoint ($p = .10$).

Several methodological problems exist in the Svendsen report. One problem is possible misclassification of husband's smoking status either at entry or subsequently. A second problem is that the wife's smoking status was based on interviews with the husband, and not on direct questioning of the wife.

There is also an alcohol-related bias, as MRFIT ETS-exposed husbands' had two drinks per week, on average, more than non-ETS exposed husbands, and this alcohol effect could explain the observed statistical significance in dose response.

Finally, by combining ex-smoking husbands with never smokers, Svendsen confounds any past effects of active smoking by the husband with exposure to ETS.

The MRFIT study serves as an exemplary prospective trial for its design and conduct. However, lack of statistical significance, failure to control for several confounding variables (such as alcohol consumption), misclassification, and misgrouping make it difficult to draw any conclusions from the study.

5. **Helsing.** The Helsing (1988) paper examines death certificates collected from July 1963 through July 1975 for a population living in July 1963 in Washington County, Maryland. This is based on underlying cause of death of arteriosclerotic heart disease including coronary disease (International Classification of Disease [ICD] -420) and other myocardial degeneration (ICD 422). As of July 15, 1963, 98% of the residents were asked questions that included information on sex, age, race, marital status, years of schooling, housing characteristics, information on cigarette, cigar and pipe smoking habits, as well as frequency of church attendance, for each household member aged 16.5 years or older.

Among 22,973 white men and 25,369 white women 25 years of age and

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older in the 1963 census, 4,162 men and 14,873 women reported that they had never smoked. The 1971 follow-up population was a subset of these numbers: 3,454 men and 12,345 women.

The results showed that death rates from arteriosclerotic heart disease were higher among men (relative risk = 1.31) and women (relative risk = 1.24) who lived with smokers in 1963, after adjustment for age, marital status, years of schooling and quality of housing index. For women, relative risk increased significantly ($p < .005$) with increasing levels of exposure, but for men, there was little evidence of a dose response relationship.

Several methodological problems exist with the Helsing paper. The first major problem is that the only smoking data that was collected on every person was in 1963. Hence, no changes in smoking habits over the 12-year period were ascertained. In addition, no data were collected on other risk factors for heart disease such as diet, exercise, blood pressure and cholesterol. Finally, no ETS exposure outside the home was measured.

B. Case-Control Study

1. **Lee.** The Lee (1986) study is a case control (retrospective) study to evaluate the possible relationship between cigarette smoking and risk of lung cancer, chronic bronchitis, ischemic heart disease and stroke. The original questionnaire was administered in ten hospital regions in England, between 1977 and 1982. Although not recorded initially, ETS exposure data was subsequently collected in 1979 for married patients in the last four regions.

Two hundred cases and 200 matched controls were collected for each sex (male, female) and age (35-44, 45-54, 55-64, and 65-74) grouping to examine the possible relationship between ETS exposure and diagnosis of ischemic heart disease. Also matched were hospital region and, when possible, hospital ward and time of interview.

Ischemic heart disease cases and controls did not show a statistically significant difference in their exposure to ETS, based either on smoking habits of spouses or on an index accounting for exposure at home, at work, and during travel and leisure.

Although the Lee study is one of the few to attempt to examine non-spousal ETS exposure, it raises the general methodological issues that surround retrospective case control studies. In its finding of non-statistical significance for any trends of association between ETS and cardiovascular illness, the Lee paper confirms the need for execution of better controlled prospective trials.

C. Experimental Design

1. **Aronow.** The Aronow (1978) paper describes an experimental design to examine the possible relationship between exposure to ETS and exercise-induced angina in both a well ventilated and an unventilated room.

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The design included ten men (eight non-smokers and two smokers) who exercised upright on a bicycle ergometer with a progressive work load until the onset of angina pectoris. Subjects were randomized to three groups: no smoking, smoking in a well ventilated room, or smoking in an unventilated room.

Aronow has suggested that the results of his study demonstrate that, under the conditions of the experiment, ETS exposure causes anginal pain to develop soon after exercise. In addition, the data from the study indicate that exposure to ETS causes an increase in carboxyhemoglobin, more after ETS exposure in an unventilated room than after ETS exposure in a ventilated room.

Several major criticisms of the Aronow study include: (1) the use of subjective pain as an end point without double blinding, (2) a very small sample size that can lead to a large variance based on just one or two subjects changing their responses, (3) problems associated with the Hawthorne effect [subjects tend to produce symptoms suggested to them], and (4) failure to control for stress.

D. Conclusions

The Surgeon General's Report of 1986 (1986) examined the studies of Hirayama, Gillis, Garland and Aronow, and concluded that "further studies on the relationship between involuntary smoking and cardiovascular disease are needed in order to determine whether involuntary smoking increases the risk of cardiovascular disease."

The National Research Council (1986) in 1986 reviewed the prospective studies of Garland, Gillis, Hirayama and Svendsen, as well as several experimental designs examining the biological plausibility of the association of ETS and cardiovascular disease, and concluded that:

1. No statistically significant effects of ETS exposure on heart rate or blood pressure were found in healthy men, women, and school-aged children during resting conditions. During exercise there is no difference in the cardiovascular changes for men and women between conditions of exposure to ETS and control conditions.
2. With respect to chronic cardiovascular morbidity and mortality, although biologically plausible, there is no evidence of statistically significant effects due to ETS exposure, apart from the study by Hirayama in Japan.

It is the opinion of this author that none of the studies critiqued in this paper provides any basis for altering the Surgeon General's and NAS's conclusions concerning ETS and cardiovascular disease.

This conclusion is reinforced by the findings of Schieveblein and Richter (1984). They report that, under real-life conditions, persons exposed to ETS inhale only approximately .02 to .01 of the amount of particulate matter

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taken up by active smokers. Also, nicotine concentration in serum of ETS-exposed individuals is within a range that is barely distinguishable from the background level, and the increase in carboxyhemoglobin rarely exceeds 1%. The authors conclude that exposure to ETS "is not likely to have an effect on the development and progression of CHD."

II. Recommendations for Future Research

To provide meaningful recommendations for future research, it is necessary to evaluate the existing studies of ETS exposure and cardiovascular disease in light of the five criteria for causality discussed at the beginning of this paper.

The NAS concluded that a relationship between ETS exposure and cardiovascular disease is biologically plausible, and each of the studies reviewed in this paper appears to provide an adequate temporal association between ETS exposure (as measured by spousal smoking) and the onset of cardiovascular disease. However, the studies fail to meet one or more of the remaining criteria for causality.

Of the six studies concerning ETS exposure and cardiovascular morbidity and mortality, only two (Hirayama and Helsing) reported statistically significant relative risks for exposed compared to non-exposed populations, and neither study reported a relative risk greater than 2. Hirayama reported a dose dependent relationship but Helsing did not.

None of the studies demonstrate a specificity of association between ETS exposure and cardiovascular disease. Each of the studies fails to control for one or more important confounding variables, including lifestyle, blood pressure, serum cholesterol, obesity and socioeconomic status. None of the studies provides an accurate measurement of ETS exposure. All of the studies suffer from one or more serious methodological problems, including small sample size and possible misclassification of spousal smoking status. These confounding variables and methodological problems also preclude any demonstration of consistency of association among the existing studies.

In view of the inadequacy of existing studies, it is logical to consider whether the Framingham Heart Study might provide an adequate basis for a definitive evaluation of the relationship between ETS exposure and heart disease.

The Framingham Heart Study, initiated during 1948-1950, is comprised of a study cohort from a random subsample of the adult residents of Framingham, Massachusetts, of which 69% responded. No reports on ETS and heart disease have been published under the Study, but spousal smoking habits could be determined from the Study's data base. Although an effort could be made to measure ETS effects on heart disease in the Framingham Study, this would not be likely to provide an adequate basis for a definitive evaluation of ETS and heart disease.

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The critical problem is that the Framingham Study does not provide a basis for an accurate measurement of ETS exposure, especially outside of the home. Use of data on spousal smoking habits as a surrogate for ETS exposure has been shown to present serious methodological and other problems in existing studies.

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In any event, the recent paper by Seltzer (1989) suggests that the Framingham Study is not likely to show a significant association between ETS exposure and heart disease. Seltzer's paper compares the Surgeon General's statements regarding the association between active smoking and heart disease with the data in the Framingham Study. Seltzer points out that the Framingham data differ from the Surgeon General's conclusions in several important respects:

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1. The Surgeon General asserts a four-fold greater CHD incidence in men who are heavy smokers as compared to non-smokers; Framingham reports relative risk ratios less than two.
2. The Surgeon General asserts that cigarette smoking among women has a predictive association with CHD; Framingham finds no such association.
3. The Surgeon General states there is an increase of CHD with increase of duration of smoking; in the Framingham Study, this increase is absent.
4. The Surgeon General claims that rates of CHD eventually are reduced in ex-smokers to those somewhere between smokers and non-smokers, and sometimes, after many years, falling to the level of non-smokers. The Framingham data are surprising in that reductions in CHD among ex-smokers is below levels for never smokers! This suggests that a selection bias may exist.

Given the relatively small effect of active smoking on heart disease reported in the Framingham Study, it appears unlikely that any effect of ETS exposure on heart disease could be measured under that Study.

In view of the lack of adequate existing data, future studies need to be performed that carefully examine the relationship between exposure to ETS and cardiovascular disease. It is the hope of this author that the critiques presented in this paper, examining many of the methodological problems associated with existing ETS epidemiological studies, will be of use to well-trained scientists. Familiarity with the five key points of causality in epidemiology is critical in designing studies that can clearly show whether any association exists between exposure to ETS and cardiovascular disease.

Based on the analysis in this paper, a meaningful future study should contain at least the following elements:

1. A representative sample large enough to yield adequate statistical power.
2. A design that provides control for important confounding variables, in-

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cluding blood pressure, diet, alcohol consumption, plasma cholesterol, body weight, sex, socioeconomic status and exposure to environmental substances other than ETS.

3. A mechanism for accurate measurement of ETS exposure, including exposure outside the home, and adequate follow-up of exposure status.
4. A prospective design specifically developed to satisfy the criteria for causality.

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Panel Discussion on Cardiovascular Disease

Joseph Wu: This paper is now open for discussion. Would the discussants please proceed to the desk.

We'll have the first comment by Dr. Alan Armitage.

Alan Armitage: I would like to congratulate Dr. Wexler on his succinct presentation and to say that I agree with nearly everything that he has said. There's really not too much data and with six discussants all to say their bit, I will be selective in what I say and confine my comments to essentially pharmacological matters. The big question, of course, is whether exposure to ETS represents a health risk for the development of coronary artery disease. We need to remember that CHD is, of course, a common cause of death among nonsmokers. Moreover, although the public health body considers there to be a causal relationship between active cigarette smoking and development of CHD, Seltzer in particular has pointed out much that is not wholly consistent with such a story.

Dr. Wexler referred to five criteria that need to be considered in reviewing the ETS cardiovascular data. It is a good discipline to have this checklist approach and in addition, particularly when a situation is not clear cut, as is the case for ETS and cardiovascular disease, the sensitive, unbiased reviewer needs to have a common-sense "feel for the data."

There are three points I would like to add to the debate about biological plausibility.

First, the question of dosimetry is of particular interest to me because I am a pharmacologist. As we were told this morning, the effective dose of an ETS exposed individual is a function of the dynamic integration of concentration in various environments throughout the day and the time the non-smoker spends in these environments. Assessing accurate dosage under real life conditions is therefore extremely difficult. Frankly, in many epidemiological studies, the assessment is no more than anecdotal. Merely knowing something about the spouse's or partner's smoking habits is not enough.

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Since we are considering possible effects of ETS on the cardiovascular system, we must be concerned with systemic absorption rather than mere deposition. An individual exposed to the diluted smoke which is ETS cannot and does not absorb tobacco constituents such as nicotine and carbon monoxide to any significant degree, or any other putative cardiovascular toxicant like nitrogen dioxide. Thus, cotinine levels in biological fluids, which are generally considered to be a reasonable measurement of nicotine absorption of nonsmokers exposed to ETS, are approximately one percent of those measured in active smokers.

Now, in many studies the association between active smoking and CHD is much weaker, or even nonexistent, in female smokers than in male smokers. If in female active smokers an effect of smoking on the development of CHD cannot be convincingly demonstrated, I find it difficult to believe that such an effect is possible in female nonsmokers exposed to ETS (the favored subjects for epidemiological studies), unless there is something exceptionally noxious in ETS as compared to mainstream smoke.

A second point that to me casts doubt on the possibility of any significant role of ETS in the development of CHD concerns the pipe smoker. Pipe smokers inhale tobacco smoke actively to a limited extent. They also commonly surround themselves in a cloud of tobacco smoke so that they are probably exposed to the highest concentrations of ETS of any group. Yet, they enjoy relative immunity from the three major diseases associated with active smoking.

Finally, Dr. Wexler gave us some ideas on the definitive prospective study that he believes needs to be undertaken to answer the question I posed at the beginning of my commentary. Frankly, I would like to question the need for such a study. It will cost a lot of money that would probably be better spent on other, more important public health issues, as Dr. Roe has suggested. After all, cardiovascular diseases occupied only two pages of the 1986 Surgeon General's Report on the Health Consequences of Involuntary Smoking and did not feature at all in the Fourth Report of the U.K. Independent Committee on Smoking and Health.

So my clear advice to nonsmokers, of which I am one, and to those like me who are fond of good food, is to watch your weight, watch your diet, watch your blood pressure, but don't get too hung up about ETS.

Joseph Wu: Thank you. We will now hear comments from Dr. Joseph Fleiss.

Joseph Fleiss: In general, prospective cohort studies are prone to less serious bias and are subject to fewer sources of bias than are retrospective case-control studies. (Fleiss, J.L. (1981). *Statistical Methods for Rates and Proportions* (2nd ed.) Wiley, New York.) I believe that this general contrast between the two study designs holds for the published studies of the health effects of exposure to environmental tobacco smoke, so that the overall qual-

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ity of the published studies seeking to associate exposure to ETS with coronary heart disease has been superior to the overall quality of the published studies seeking to link exposure to ETS with lung cancer. This is not to say that the former set of studies, all but one of which have been prospective, are free of bias. My comments, which do not duplicate those made by Dr. Wexler in his excellent review, shall be specific to the biases that may have affected some of the published cohort studies under consideration.

One kind of bias that should have no place in science is prejudice: deciding beforehand what the final results should be, and then making statistical decisions and expressing the results so that the conclusions turn out the way they were supposed to. Consider, however, the 1985 study by Garland et al., one of the first to have been published. An inappropriate statistical decision the authors made was to perform one-tailed tests. That is, statistical significance would be declared only if the mortality rate of ischemic heart disease among nonsmoking women married to smokers was significantly greater than the mortality rate from ischemic heart disease among nonsmoking women married to nonsmokers. A difference in the other direction was ruled out a priori as either unimportant or unbelievable: "Since we were testing previous findings concerning the risk of passive smoking, statistical significance was assessed at one-sided p levels."

Their reasoning is flawed. The authors were not retesting previous findings. They were testing, for the first time as far as they knew, an association with ischemic heart disease. They were apparently unaware of the chapter by Hirayama that had appeared a year earlier (Hirayama, 1984). Even if theirs was the tenth study of the effect of ETS on ischemic heart disease, and even if each of the preceding nine showed a significant excess incidence in the group exposed to ETS, an attitude of open-mindedness would have led them to a two-tailed test.

I was sorry to see sanction given to one-tailed tests in the 1986 Surgeon General's report on ETS: "Given the strength of the evidence on active smoking and disease risk, one-sided testing in the direction of an adverse effect seems appropriate for most potential consequences of ETS." I have argued publicly that one-tailed tests are almost never appropriate in randomized clinical trials (Fleiss, J.L. (1987). Some thoughts on two-tailed tests. *Control Clin. Trials* 8: 394; Fleiss, J.L. (1989) One-tailed versus two tailed tests: Rebuttal. *Control Clin. Trials* 10: 227-230.), and do not see any valid reasons to excuse epidemiological studies from the requirement for two-tailed tests. More is at stake than the impossibility, with a one-tailed test, of ever finding that nonsmokers exposed to ETS might be at significantly less risk than those not exposed. Biased decisions might be made concerning which potential confounding variables to control for and which not if a difference in the "wrong" direction has been ruled out: a potential confounder that moves the odds ratio or hazard ratio in the hypothesized direction may be more likely

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to be included in the analysis than one that moves the measure of association in the "impossible" or "unimportant" direction. I am not suggesting that this kind of error actually occurred, only that preconceptions as to the possible direction of association invite biased judgments.

After adjusting for differences between the exposed and unexposed cohorts in risk factors for heart disease, Garland et al. found the relative risk for death from ischemic heart disease to be 2.7, with a one-tailed p-value less than 0.10. (Recall that this corresponds to a traditional two-tailed p-value of $p < 0.20$.) The authors concluded that "these data are compatible with the hypothesis that passive cigarette smoking carries an excess risk of fatal ischemic heart disease." Not stated is the fact that the range of uncertainty is so great (the 95% confidence intervals for the relative risk extends from approximately 0.6 to over 12.0) that the data are also compatible with no excess risk and with a markedly reduced risk of fatal ischemic heart disease among those exposed to ETS. Data that are compatible with so many contradictory hypotheses are really compatible with no hypothesis.

The statistical criteria used by Svendsen et al. in their 1987 paper were more appropriate than those used by Garland et al. But the statement of their major conclusion reveals a similar possibility of prejudgment: "Our findings . . . support the hypothesis that passive smoking is associated with an increase in morbidity and mortality among nonsmokers." The only morbidity studied by the authors was coronary heart disease morbidity, and it was analyzed only in conjunction with coronary heart disease mortality. None of the relative risks for the composite endpoint of fatal or nonfatal coronary heart disease was significant at the 0.05 level, even without control for multiple comparison artifacts. Once again, the findings support a number of difference hypotheses, not just the one stated by the authors.

I mentioned a 1984 chapter by Hirayama in which, apparently for the first time, a statistically significant association was reported between a non-smoking women's exposure to ETS and her risk of dying from ischemic heart disease. There are several problems with Hirayama's analyses. One concerns his erroneously presenting values of critical ratios as values of chi-square. The problem is not a trivial one because the same error was pointed out to him some years earlier in letters written in response to his initial paper linking exposure of ETS with lung cancer (Hirayama, 1981). Another example of possible sloppiness is found in one of his tables (Table 7). When numbers of deaths are first subdivided by the spouse's age group, and are then subdivided by the spouse's age group as well as the spouse's occupation, one expects some reduction in the numbers because of missing data. The last thing one expects are increases in the numbers; that is, more deaths with information on two characteristics than with information on one. Nevertheless, this is exactly what happened.

One must wonder what other statistical mistakes Hirayama has persisted

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in making. Consider his persistence in controlling for the age of the husband when analyzing data for the wife. This curious and basically indefensible feature of his analytic strategy was also pointed out to him in the correspondence that followed his first paper (Hirayama, 1981) but he never responded adequately. The reason wasn't the unavailability of the wife's age because he finally presented results for lung cancer that controlled for the wife's age in the same chapter in which he presented his results for ischemic heart disease (see his Table 2 on p. 180).

A striking feature of Hirayama's data for ischemic heart disease mortality in nonsmoking wives is that an association with the husband's smoking emerges only after the husband's age is adjusted for:

Smoking Habit of Husband	Odds Ratio*	
	Before Adjustment	After Adjustment
Ex-smoker or 1-19 per day	1.01	1.10 (n.s.)
More than 20 per day	0.99	1.31 ($p < 0.05$)

*Versus nonsmoking husbands as the control group.

Until Hirayama analyzes his heart disease data sensibly by adjusting for the effect of the wife's age and not her husband's, and adjusting for the effects of other confounders, I suggest that his findings not be taken seriously.

Peter Lee: Dr. Wexler gave a careful presentation on ETS and cardiovascular disease and I agree completely with his conclusion that the existing epidemiological evidence is inadequate to provide proof of a cause and effect relationship.

I would like to draw attention to a number of points that may assist discussion of this important issue. First, I would like to point out that there is, in fact, a small amount of information in addition to that cited by Dr. Wexler. In his 1988 meta-analysis paper, Wells reports the results of a non-published 1986 study by Martin et al. in Utah purporting to find a statistically significant relative risk of 2.6 despite being based on a total of only twenty-three deaths or cases of CHD. (Wells, A.J. (1988). An estimate of adult mortality in the United States from passive smoking. *Environment Int.* 14: 249-265.)

So we've actually got seven epidemiological studies, six of which report a positive association. Of the six, four of them, Hirayama, Helsing, Martin and Hole report a statistically significant result, either in trend analysis or in simple comparison of ETS-exposed and non-exposed subjects. Garland, Hole, Martin and Svendsen report a relative risk in excess of two (more than a 100% increase in risk) in relation to ETS exposure. In comparison, a mass

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of literature from large prospective studies shows that active smoking, on average, is associated only with a 60% to 80% increase in risk of heart disease. Given that ETS-exposed nonsmokers are far less exposed to smoke constituents than are active smokers, and also that active smokers have more ETS exposure than ETS-exposed nonsmokers, these results just seem to me to lack plausibility, a priori. They seem far more likely to result from chance or bias than to represent a real effect.

One form of bias that may be particularly important in assessing the relationship between ETS and heart disease is the possibility of publication bias. When you look at the overall literature you see that the total number of reported deaths or cases in ETS studies involving heart disease is similar to those involving lung cancer. When one considers that the incidence of heart disease death in nonsmokers is vastly more common than lung cancer deaths in nonsmokers by a factor of about fifty, it's really rather surprising that so few even moderately sized studies of heart disease and ETS have been published.

Dr. Wexler suggests that the Framingham study might be able to provide data, but really this is only a relatively small study of a few thousand people. Surely the most obvious place to look for more information is the American Cancer Society's Million Person Study. They have published results on ETS and lung cancer involving a hundred and fifty-three deaths. (Garfinkel L. (1981). Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *J. Natl. Cancer Inst.* 66: 1061-1066.) They certainly have the information to publish results on ETS and heart disease involving, I would imagine, five to ten thousand deaths. The obvious question arises, does failure to publish mean no association was found? Because if that in fact were the case, this would cause an absolutely enormous distortion of the overall evidence.

If you look at the seven published studies on ETS and heart disease, only Helsing's and Hirayama's are based on any sort of substantial numbers of deaths at all. I just want to add a few points regarding these two studies.

First, I note some further weaknesses in the Helsing study. There was no adjustment for number of people in the household. Helsing was comparing people who lived with a smoker and those who did not. So, for instance, people who lived on their own automatically went into the category of people who didn't live with a smoker. There's obvious scope for confounding with factors relating to living alone, overcrowding, etc. The study was also not actually about the probability of dying but about the probability of dying within Washington County, as I understand it. They made no attempt to get death certificates for people who moved outside this relatively small area of the United States. If smoking, ETS exposure or household size related to the probability of leaving the county, bias would result. In contrast, I noticed in the British doctors' study that they took enormous pains to follow up the thirty thousand or so doctors involved. They chased people to the ends of the

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globe to find out what they died of and I think they only failed to track down fifty or sixty, mainly those doctors who had gone back to India and had gotten lost in the subcontinent somewhere.

The Helsing study also used statistical adjustments by a procedure that wasn't really clear and which had an enormous effect on the relative risk estimates. In women he had an unadjusted 34% reduction in risk which he put through his magical unexplained statistical machine and got a 24% increase. So I'd really like to see rather more before accepting anything from this study.

The only other study with substantially more than 100 deaths is that of Hirayama. Dr. Wexler's paper dealt at length with the weaknesses of this study and he quoted the results on the first two lines in his text. The fact that there was a nonsignificant relationship in 1981 and a significant relationship in 1984 is intriguing. The first result was based on 404 deaths, the next on a further 88, and the analysis was essentially the same apart from the fact that in the first analysis he standardized for age and occupation, in the second analysis, only for age.

Now, if you assume occupational standardization made no difference, you can actually calculate what the relative risks were for the intervening period. You've got this enormously strong relative risk of five. You can also show that there's very highly significant heterogeneity of relative risk between the first period up to 1981 and the period thereafter. But if, in fact, you can't do this because standardization of occupation did have an effect, well why on earth didn't Hirayama standardize for it in 1984? So it seems not to make sense either way.

The question finally is whether a new study is actually worth doing. Dr. Wexler noted that existing data are inadequate for proof of cause and effect and proposed that a large study be carried out. The problem, it seems to me, is that given what we know about the association of active smoking with heart disease and the relative exposure to ETS of nonsmokers, it seems highly implausible that even in the most ETS-exposed nonsmokers you get a relative risk of more than two. I believe Dr. Wexler said in his paper that he feels one actually requires a relative risk of two or more as a precondition to prove causality.

So if that's the case, what's the point of doing the study? Although I believe that a good study can pick up relative risks of less than two, I have my doubts that any study could pick up an effect of the order of magnitude which could plausibly exist in this case.

Joseph Wu: Comments by Dr. Lorimer?

Ross Lorimer: The studies that Dr. Wexler very ably and very extensively reviewed are a testimony to the diligence of medical investigators. More than 100,000 individuals have been assessed from the point of view of cardiovascular disease and ETS and we still have no definite answers, although we do have some impressions.

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The question of a meta-analysis of results has been considered. Certainly, the Surgeon General's report of 1986 suggested this possibility. Further data have accumulated since then. From the cardiological point of view, there is no doubt that in certain situations meta-analysis has been useful. For example, the use of beta blockade following myocardial infarction has been well substantiated by the use of meta-analysis. The effect of lowering cholesterol levels on the subsequent incidence of coronary heart disease has been shown to be a worthwhile clinical exercise by this method. These studies have employed finite end points, such as survival, and variables, such as cholesterol levels, which can be standardized. Under these circumstances, it is relatively easy for different populations to be compared. However, meta-analysis of the relationship between cardiovascular disease and ETS involves comparing such disparate groups as an agricultural population of Japanese women with a group of Californian women living in a retirement community. The MRFIT/ETS study evaluates American men who are already at increased risk from coronary disease because of raised cholesterol and high blood pressure. This would be compared with a group of men and women with a different range of risk factors living in the environment of the west of Scotland. In these situations, it may be that meta-analysis is not appropriate.

There has been considerable discussion today regarding the Hole study from the west of Scotland. I would like to review their data regarding coronary heart disease deaths. In the control group, there were index case nonsmokers living with nonsmokers. In the ETS exposed group-index case nonsmokers were living with cigarette smokers. The single exposure group were index case smokers living with nonsmokers and in the double exposure group both co-habitants smoked. There were 30 deaths from coronary heart disease in the control group where neither partner smoked. On a pro rata numerical basis one might have anticipated around 48 to 49 deaths in the ETS exposed group. Fifty-four deaths did occur, an excess of only five or six. It is important, however, to recognize that correction of data for age, sex, blood pressure, cholesterol and social class did show a significant increase ($p < 0.008$) for relative risk of coronary heart disease. In the MRFIT study, on a pro rata basis there would appear to be two excess deaths from coronary heart disease and four extra myocardial infarctions. Again, this was a study involving a large number of people followed for around seven and a half years and statistical analysis did suggest an association between ETS and coronary heart disease, although this did not achieve formal statistical significance.

While we can discuss the merits or demerits of the various statistical approaches, it would appear that the actual number of extra deaths is relatively small. From the clinical point of view, I would agree with Dr. Armitage that the important factors with regard to coronary disease are active cigarette smoking, high blood pressure, high cholesterol, life style, and employment or unemployment. There may well be other factors involved. However, it seems

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unlikely that ETS is contributing significantly to the incidence of coronary heart disease. I would also think it unlikely that it would be possible to confirm or refute this suggestion by mounting a further long-term study. The studies report a small adverse association of ETS and coronary heart disease at most. Any further study would require an extremely large population followed for a very long period of time. This simply may not be possible as a practical matter.

Joseph Wu: We now have comments from Dr. Max Weetman.

Max Weetman: I've had this all my life, beginning with "W" and having most functions in life allocated according to the starting letter of your name. Everything's been said. I've really got very little to add. I'd like to congratulate Dr. Wexler on a really very thorough job of going through the various cases.

I think most of the points have been made here, but I've not come as far as this to actually say nothing, so I want to consider a new "ology". We've talked epidemiology, dosology, and things of this nature. But there's really a rather more fundamental "ology" that we ought to consider, and that's epistemology.

Epistemology is what can we know, what is knowable.

We can't know very much about ETS and cardiovascular diseases, I think, because of the problems I will outline here. I would consider all of these problems to be design problems. I'm not going to go through all of them in fine detail, but I have a few points I want to make. Everything I say here applies equally to cancer of the lung as well.

The first weakness really stems from our measurement of exposure to ETS. The best way to control this would be to experiment in a reaction chamber, where you can actually monitor certain surrogates for environmental tobacco smoke and control the number of cigarettes smoked.

Once you go beyond this, to a real world situation, or into a retrospective look at somebody's lifestyle, epidemiology begins to lose all credibility. It's really guessology with respect to exposure at this stage.

Now, how do we actually find out about what possible exposure one might have suffered? We do it by asking people. We ask, "Did you smoke? Did your husband smoke? Did your wife smoke?" etc. Obviously, this approach is prone to an enormous degree of error. We're not likely to get a particularly accurate and true answer there.

Another problem, particularly true for studies of cardiovascular disease, is the use of selected populations. Taking the Multiple Risk Factor Intervention Trial, for example, the patients had high serum cholesterol levels and high blood pressure. In addition, they drank rather more than the control group. Why do we rely on this high risk group for information? Perhaps it's going to tell us something that "normal people"—whatever that might mean—wouldn't.

The second trial where we get some positive information is the noto-

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rious—I would say—Hirayama trial. There are even more things wrong with it than have been said here. It's tremendously unrepresentative of the population of Japan because it includes far too few old people, over eighty.

Now, why do we use these peculiar things, the Japanese or high risk or atypical groups, like Hirayama's Japanese cohort or those in the MRFIT? It's because ETS as a problem is quite a recent event. It started with Trichopoulos and Hirayama himself in about 1981. Most of the trials considered today did not originate as studies of exposure to ETS, but as studies of other phenomenon, that have been adapted to consider ETS.

The Multiple Risk Factor Intervention Trial had been running for some time. Hirayama's trial was already about twelve or thirteen years old before he started to seek information about ETS exposure.

Epistemologically speaking, the result of this is that you are preselecting the study group, so you have too few subjects to resolve the question. The Garland trial had two deaths in the control group. It's far too brittle a number for a baseline. You can't draw any conclusions about common disease from such small groups.

The use of death certificates is another problem. Not all the trials use death certificates. There are some exemplary attempts where physicians actually review the case to determine the likely cause of death and guard against error. But a lot of the trials, including Hirayama's, use a death certificate only. These are, we know, notoriously inaccurate.

Now, the only thing I would really argue about with our eminent opening speaker involves a little bit of philosophy; I'm talking about biological plausibility. Asking questions about biological plausibility can sometimes be misleading. The worst case arises when you've got a rather weak P-value: you're not quite there but you obviously would like to get there. You then list a number of factors that, had you continued, would have caused you to reach the desired result. You then ask, is it a biologically plausible event that this result will occur? To me, if biological plausibility is used in this sense, it really means "in the absence of evidence, I will now cast one further card, a weak one though it be." The purpose is to fit the results to the preconception brought by the scientist to the experiment. As has already been said, this is the antithesis of scientific investigation. It's wish fulfillment. Maybe our grant bodies are partly responsible for this. We have to publish more and more papers, even though some of them may be nonsense, so that we can obtain the next grant, and do the next run of work.

Similarly, with respect to biological plausibility, Peter Lee has very clearly pointed out that if you have eight factories in quite different places, and people die from some rare disease all having been involved in the same industrial process, you don't say, "Well, I can't see how it's working biologically." If you think about what we know biologically, most things are absurd in the first

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place, and the rationality in which we place them comes after the initiating discovery.

This is certainly true for most new types of drugs that are discovered. It's interesting to note that carbonic anhydrase had been demonstrated in the stomach many years ago, and was only then discovered in the kidney when they first used sulfonamides and obtained a diuretic response. The only way you could explain this diuretic response was by actually postulating that this enzyme was there and sulfonamides inhibited it. So quite often you get something amazing, biologically implausible and that then promotes discoveries that result in a rational background being discovered.

I think a more economical phrase that we ought to try and use, if we have to be stuck with this notion of biological plausibility, is "freedom from biological implausibility." That's putting the boot on the other foot and asking people to do a little bit of thinking rather than just justifying their original thoughts.

Joseph Wu: We'll have the comments from Dr. Philip Witorsch.

Philip Witorsch: Like Max Weetman, I've spent most of my life being at the end of the list. I therefore decided to comment briefly on an aspect that none of the other speakers has addressed, namely the acute effects of ETS exposure on individuals with pre-existing coronary artery disease. Dr. Wexler very eloquently critiqued the Aronow study but there is another, very good study that was published in 1987 by Sheps et al. from the University of North Carolina. The Sheps study raises the issue of the biological implausibility of the acute effects postulated by Aronow.

Aronow and others have suggested that the acute effects of ETS exposure with regard to exacerbation of angina in individuals with pre-existing coronary artery disease relate, at least partially, to elevation of carboxyhaemoglobin from ETS exposure. Superficially, this sounds like it might make sense, until you think about the amount of carbon monoxide actually generated from ETS. Studies have shown only a slight difference in the levels of carboxyhaemoglobin in nonsmokers exposed to ETS as compared to those in nonsmokers not exposed. This result causes the hypothesis to lose its plausibility.

The Sheps study examined thirty individuals with well-documented coronary artery disease and symptomatic angina who had documentation of electrocardiographic changes on exercise typical of angina. They exposed these individuals in an exposure chamber to carbon monoxide, using an endpoint of approximately four percent carboxyhaemoglobin. That compares to levels usually found in nonsmokers and in their controls of about 1.5% carboxyhaemoglobin.

Interestingly, to achieve the 4% carboxyhaemoglobin they had to expose their subjects to one hundred parts per million of carbon monoxide in air for a period of an hour or more. This is probably three to five times the level of

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carbon monoxide that has been measured in very smoke-polluted areas. They exercised these individuals and measured a variety of cardiovascular parameters, including electrocardiographic evidence of angina, ST-T wave changes, radionuclide imaging of the heart, ejection fraction, and a number of other cardiovascular indices.

They found absolutely no effect on the duration to onset of angina, or any of the objective cardiovascular parameters, despite the subjects' exposure to a hundred parts per million of carbon monoxide and a carboxyhaemoglobin level approaching four percent.

The Sheps study, when added to all the deficiencies cited relative to the Aronow study, should lay this issue to rest. It's very clear that in a real-life situation it is biologically implausible for the degree of carbon monoxide exposure related to ETS to have any effect as far as exacerbation of angina.

I think this might have implications for studies of ETS and reproductive effects as well. Frank Sullivan mentioned earlier that carboxyhaemoglobin is thought possibly to play a role relative to reproductive effects. But it appears implausible that the degree of real-life exposure to ETS results in any significant changes in carboxyhaemoglobin.

Joseph Wu: We have time for a couple of additional comments or questions from the floor. Dr. Roe.

Francis Roe: If I could just address a question to the panel in general. I have the impression that coronary heart disease is not a single disease but at least two. Coronary heart disease in men under the age of fifty seems to be related to different factors than CHD occurring from age sixty onwards. These seem to be two different diseases, but maybe there are many others. I wonder what the implications of this are in relation to studies of ETS.

Secondly, from a causative point of view, one would be concerned with two things. The first is the set of factors that cause arteriosclerosis, and the second is the set of factors that make a fatal coronary occlusion more likely in a person with arteriosclerosis. They seem to be two different things. Aronow obviously was looking at the second of these. The first should not be overlooked.

In examining carcinogenesis, I earlier stressed the point that you need to know what an individual has been exposed to from childhood in order to get any reliable feeling of what happens in lung cancer risk. I suggested that this has not been done so far.

Now, isn't this also true of cardiovascular disease? I mean, the idea of Aronow collecting a lot of old gentlemen and sticking them all on exercise bicycles, to me, is horrific. Would we not be better off if we really started such studies with younger people?

Peter Lee: I would comment on the second of Dr. Roe's points. I suspect lifetime exposure isn't so important in heart disease as it is in respiratory disease. If one takes the analog of active smoking, the evidence seems to

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suggest that current smoking is important and ex-smoking is not really important because if you give up smoking, your risk reverts fairly quickly. Yet, there may still be something in it even so.

Ross Lorimer: A similar problem arises in studies of women. Coronary artery disease in women expresses itself differently than in men insofar as pre-menopausal women are concerned. From a clinical point of view, the coronary heart disease occurring in women also is usually associated with much smaller diameter of coronary vessels with more diffuse disease than in young men with myocardial infarction, in whom it is not unusual to find single vessel disease, especially involving the left anterior descending and having an acute thrombotic episode. So I'm sure you're absolutely right.

Philip Witorsch: If I can just add a brief comment. I agree that there are different diseases involved. I think lifetime factors are important, but not necessarily lifetime ETS exposure or lifetime cigarette smoking. In many of these studies, people tend to forget that perhaps the most important determinant of coronary artery disease is the choice of parents that one makes. Added to that are diet, lifestyle, exercise and a whole host of other factors, all of which have been very poorly controlled for in the studies to date and are, frankly, very difficult to control for. Assessing cholesterol levels is not an adequate control of many of these factors and that's, perhaps, the most that's been done. It's very analogous to the token control for socio-economic status that has been done in a lot of studies.

Jarnail Singh: I have been doing research on the effect of carbon monoxide levels in animals since 1972. I have a series of papers and a series of experiments where I expose mice from when they are newly born, three, four days old, until they are about eight weeks old. The mice are constantly exposed, except during cleaning and watering, to three levels of CO, 25 PPM, 50 PPM and 100 PPM. At the end of eight weeks, we sacrifice the animals, take all the tissues, lungs, hearts, spleen and kidney, and send them to a pathologist to determine whether there is any dose-dependent effect on these organs. The conclusion is that at these levels, 25, 50 and 100 PPM, there is no dose-dependent effect on the heart or on the lungs.

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INDOOR AIR QUALITY AND VENTILATION

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ENVIRONMENTAL TOBACCO SMOKE (ETS) AND CARDIOVASCULAR DISEASE

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ABSTRACT

The epidemiological evidence relating exposure to ETS and cardiovascular diseases has been examined: all of it is flawed. Most of the difficulties arise from the different study designs. Three of six studies report an increased RR for cardiovascular diseases, although the others failed to do so. It is concluded that no increased RR has been established unequivocally, either because there is none, or because the inadequate design of the studies frustrated their objective.

INTRODUCTION

Exposure to environmental tobacco smoke (ETS) has been associated with a number of serious diseases in man. In virtually all cases, it has not been possible to simulate in animal models the adverse health effects reported in man, so the evidence depends upon the findings of epidemiological studies. There is distinct weakness in the design of these studies, some of which are peculiar to the evaluation of effects of ETS (1), and others which are common to all epidemiological investigations (2). With respect to ETS, two factors prevent us reaching unambiguous answers; first, there is the poor assessment of the extent of exposure (3), and secondly, there is the misclassification of some cigarette smokers or ex-smokers as non-smokers (4).

In the report of the Surgeon General (5), less than 2 of 359 pages are dedicated to ETS and cardiovascular disease. In another comparable review, conducted by the New York Academy of Science (3), only 11 of 337 pages refer to cardiovascular diseases. The present paper considers six epidemiological studies identified in an extensive search of the literature (6-11).

The first thing to note from this database is that the majority of the studies were not designed specifically to investigate the effects of ETS exposure on the incidence of cardiovascular disease, but were adapted to this purpose from some other, once the initial claims that ETS affects health adversely had appeared in 1981-2 (see 12, 13). This adaptation of existing studies has led to effects being sought in populations that are not representative of the population at large.

How is exposure to ETS quantified? No substance is known that

is representative of all the components of ETS (3)), so it is not possible to monitor such exposure in a meaningful manner. Instead, epidemiologists have to resort to some subjective index of exposure, usually in the form of the smoking behaviour of couples living together. In most studies, the incidence of a specific medical outcome is determined in a group of non-smokers married to cigarette smokers, and this rate is then compared with that in non-smokers married to non-smokers. In this way, exposure to ETS in the home can be assessed, although no allowance is made for exposure of both groups to ETS outside the home, or for any effects arising from exposure to other, potentially toxic, agents. It seems likely that any effects of ETS, if there are any, would be masked by the variability introduced by these confounding influences.

The smoking status of the participants in epidemiological studies is determined from questionnaires. The reliability of the answers to the questions that constitutes this part of the experimental design is low. It is inevitable that some subjects are misclassified with respect to their cigarette smoking behaviour; this probably results from simple failures in memory, or is the consequence of giving false answers to avoid admitting that they have a habit which is considered to be socially undesirable.

All the reports considered in this review have appeared since 1985, i.e. after the first suggestion in (1981) that exposure to ETS may be associated with serious health problems (12,13). However, the measurements on the subjects in the trials were made in the 1970s, i.e. retrospectively, and thus can be considered to be the result of data dredging.

REVIEW

The Garland *et al* study (8) was performed over a 10 year period after enrolment between 1972 and 1974 of 821 of the adults aged between 50 and 79 in a community of San Diego, in the U.S.A. In the period under consideration, there were 19 deaths from ischaemic heart disease (determined by analysis of death certificates). Only two deaths were recorded in the control group (non-smokers married to non-smokers), which probably represents too low a baseline level to permit safe predictions from these data to the population at large. The age-adjusted death rates for ischaemic heart disease were not significantly elevated in the subjects considered to be exposed to ETS ($P > 0.1$), and were higher in those married to ex-smokers than in those married to current smokers.

The investigation reported by Lee *et al* (11) was a case-control study initially designed to examine lung cancer risk. With respect to ischaemic heart disease, no statistically significant increased risk was associated with supposed exposure to ETS in the home, at work, or from travel and leisure.

Svensson *et al* (9) selected a sub-group of patients for analysis from the cohort in the multiple risk factor intervention trial (MRFIT). MRFIT was designed to measure the effect of different interventions on mortality of patients identified as being at high risk of coronary heart disease. Men aged 35 to 57 years old were recruited in 18 cities in the U.S.A., and followed

for a mean time of seven years. The smoking status of the cohort was determined by questionnaire and, unusually for such studies, confirmed by objective measures (i.e. measurement of serum thiocyanate levels and exhaled carbon monoxide); the cause of death was determined by a committee of three cardiologists reviewing the case-papers on a blind basis (i.e. not aware of the treatment assignment, or, in this case, the spousal smoking status). There was a small apparent increased relative risk associated with exposure to ETS in the home, but this did not reach the level of statistical significance ($P > 0.05$ for all comparisons, except for death from any cause, when $P = 0.01$). This very carefully conducted investigation was characterised by the small size of the groups under consideration (controls 56 non-fatal and fatal events in 959 subjects; spouse smokers 26 events in 286 subjects), and the sub-group selected may have been atypical, because it was chosen from the highest 15% of those at risk from cardiovascular disease.

Helsing *et al* (7) considered a population of 91,909 white people from Washington County, Maryland, U.S.A. aged 25 or older on entry in July 1963. Smoking status was determined from responses made to a private census conducted in 1963, i.e. before the publication of the Surgeon General's first report in 1964 (14), and then allocated a score on the basis of the extent of smoking, whether or not it was current, and the type of tobacco consumed (cigarette, pipe or cigar). The population was followed for 12 years, with the cause of all deaths determined from death certificates. There were 2022 deaths from arteriosclerotic heart disease in non-smokers. The adjusted (for age, marital status, years of schooling and quality of housing) rates of death from arteriosclerotic heart disease of the population was then assessed with respect to exposure to ETS in the home; a statistically significant relative risk was detected for both men (1.31, 95% confidence limits 1.1-1.6) and women (1.24, 95% confidence limits 1.1-1.4). However, it was not possible to demonstrate any increase in risk with increased exposure in men, but there was such a relationship in women ($P < 0.005$).

The study of Helsing *et al* can be criticised in a number of ways. First, the smoking status of the subjects was determined once in 1963, so there was no possibility of allowing for any subsequent changes in behaviour. Secondly, there was no information on the established risk factors for the disease, such as blood pressure and serum cholesterol levels in the exposed and unexposed groups. Finally, the end-point used in the study relied on death certificates, which are prone to considerable inaccuracy (15).

The Gillis *et al* study (6, 16) was set up in 1972-76 in Renfrew and Paisley in an attempt to detect any special circumstances that may relate to the very high rates of lung cancer and cardiovascular disease that occur in the west of Scotland. Men and women between the ages of 46 and 64 were recruited and smoking behaviour determined from a self-administered questionnaire, and subsequently checked by an experienced interviewer when the subjects attended a screening centre. A cohort of 15399 subjects was identified (80% of those qualified to participate), and followed for an average of 11.5 years. Cause of death was determined from death certificates. From these data, it was

possible to calculate the relative risk associated with exposure to ETS in the home. The only statistically significant RR was for ischaemic heart disease in non-smokers (2.01, $P = 0.008$), which is a remarkably high value, because the RR from smoking was only 2.27. There were 30 deaths in the control group and 54 in those considered to be exposed to ETS in their homes. When cardiovascular symptoms were detected in the screening component of this study, there were no statistically significant differences between the exposed and unexposed groups with respect to engine and major abnormalities of the electrocardiogram. It is possible that the ischaemic heart disease mortality rate for those considered to be exposed to ETS represents a spurious finding, because of the absence of any effect on the pre-terminal cardiovascular symptoms, and because of the magnitude of the effect relative to that seen in smokers.

The final study in this database is the one from Japan, described by Hirayama (10). A prospective epidemiological study on a cohort of 265,118 Japanese people was initiated in 1966, with a view to determining the incidence of serious disease. The cause of death used as an end point in the investigation was taken from death certificates. This study led to the first suggestion that exposure to ETS was associated with an increased risk of lung cancer (13); further consideration has resulted in additional claims of adverse health effects due to spousal cigarette smoking, including a RR of 1.31 for ischaemic heart disease ($P < 0.019$) in non-smoking women in 1984 (17). This is a surprising finding, because a report three years earlier on the same cohort led to the conclusion that "passive smoking did not seem to increase the risk of developing ischaemic heart disease" (13).

The importance of Hirayama's various reports in the field of adverse health effects of ETS cannot be underestimated. Unfortunately, most of the influence has arisen from a poorly designed study, which has been much criticised, partly because of the unclear way it has been presented in the literature. The cohort was assembled as a convenient sample, rather than as a representative one, which has resulted in over-dependence on certain categories of the population at large, e.g. agricultural workers and young people (only 2% were over 60, whereas 12% of the Japanese population fall into this category). Japanese women spend much of their time in small rooms, where any effect of ETS would be greater than in the larger indoor air spaces frequented by those who live in the west. The cooking habits of the wives of Japanese agricultural workers may have confounded the study, because kerosene stoves would have been used extensively, and these are known to emit large quantities of potentially toxic gasses and particulate matter (18). The misclassification of smokers and ex-smokers of cigarettes as non-smokers may also have contributed to the empirical findings. No doubt the influence of many of these factors could have been taken into account in evaluating the validity of the results, but this has not been possible because Hirayama has refused to give other epidemiologists access to his data (19). Such secrecy does not inspire confidence in the objectivity of the conclusions reached in the Japanese study.

CONCLUSIONS

Of the six studies considered here, only three revealed any significant effects. Each of the positive studies was flawed in some way. Two consistent problems are apparent: too strong a reliance on the accuracy of death certificates, and the unreliability surrounding the determination of the smoking status of the subjects and their spouses in order to measure of exposure to ETS. It is concluded that no increased risk of cardiovascular disease can be associated unequivocally with exposure to ETS, and it seems probable that this will continue to be the case until specifically designed trials are instigated, and some objective measure of degree of exposure can be devised.

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Indoor Air Quality in Asia

*Proceedings of the International Conference held at the
Central Plaza Hotel, Bangkok, Thailand on 28-29th
November, 1991.*

Edited by: B.R. Reverente
D. F. Weetman
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Edited by

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A CRITIQUE OF THE METHODS USED TO ASSESS THE TOXIC EFFECTS ON MAN OF COMBUSTION PRODUCTS.

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Key Words: combustion products, epidemiology, risk assessment, environmental tobacco smoke, cardiovascular diseases.

ABSTRACT

Combustion of organic material results in the release of particles, gases, and pyrolytic products, all of which can accumulate in the indoor environment, and could damage health. The methods of assessing risk to man are reviewed, and it is concluded that epidemiology provides the best single approach. The problems in interpretation of epidemiological studies are reviewed, with particular emphasis on the specific problem of environmental tobacco smoke (ETS) and cardiovascular disease. It is concluded that too many important potentially confounding factors have been overlooked to decide if there is an association between exposure to ETS and cardiovascular diseases.

NATURE AND SOURCE OF COMBUSTION PRODUCTS

It is difficult to imagine life without combustion. In addition to domestic heating, combustion of some form of fuel occurs in cooking, many forms of transportation, most industrial processes and most of the generation of electrical power. The common factor is that some form of fuel is burnt, and the fuel is derived from organic matter, with the inevitable release of pollutants. Not all combustion contributes pollutants to the indoor environment, but in those situations where this effect appears to be minimal, it should be remembered that the indoor air is derived from that outdoors, so the dirtier the air outside a building, the more polluted it will be inside.

When organic matter is burnt, three classes of pollutant are formed. First there are gases. As the predominant chemical process is oxidation, which usually occurs without sufficient oxygen to allow complete oxidation, there is the release of a complex mixture of oxides. Thus amongst the gases generated by combustion, there are oxides of carbon, nitrogen and sulphur.

Organic molecules can undergo complex re-arrangements without the consumption of oxygen in a process called pyrolysis, which is largely determined by the temperature of combustion. Finally, there is the generation of particles, which are the small globules of organic matter that give rise to the visibility of smoke. Particles vary in size, and undergo complex changes in shape and surface area when they cool down to the ambient temperature. Large particles do not stay suspended in the air for long. Particles up to $10\mu\text{m}$ are readily inhaled, and may not be rapidly cleared by from the lung; large particles ($10\mu\text{m}$ aerodynamic diameter) are deposited in the upper respiratory tract, whereas small ones ($0.1\mu\text{m}$) are exhaled [1]. The important aerodynamic diameter with respect to potential pulmonary toxicity is probably about $0.5\mu\text{m}$ [1]. Much the same mixture of gases, pyrolytic products and particles are generated from the combustion of any organic matter. For example, there is more similarity than difference in the products released from burning wood and tobacco. With combustion of organic matter that has undergone some degree of metamorphosis, as with coal, oil and natural gas, there is variation in the proportions of components generated from each, but again there is a mixture of gases, pyrolytic products and particles.

METHODS OF RISK DETERMINATION

The purpose of determining the risk to man from combustion products arises from the ubiquitous distribution of these substances. Scientific knowledge is sought because of man's insatiable curiosity, but increasingly scientists have to justify the funds they consume, so there need to be an acceptable purpose of the investigations. Any reliable findings about risks to the health from combustion products can be used in attempts to regulate levels of the offending substances, and thus protect man.

Laboratory Studies

Laboratory animals can be exposed to smoke and then assessed for any effect. However, this type of experimentation is fraught with difficulty. There is always some carbon monoxide generated by combustion, which prevents high doses of smoke being administered. The anatomy of the respiratory system of, say, rats is quite different from that of man, so it is difficult to predict the outcome in this latter species from effects seen in the former. Any experience of pharmaceutical research teaches that there is no completely reliable way of translating effects seen in laboratory animals to man. To determine what happens in man, it is necessary to investigate in man.

Direct experimentation in man can be achieved in exposure chambers. The problems here are that exposure must be short-term, and there is still an upper

limit to the dose. In the course, it is possible to expose volunteers in the laboratory, but then it is because of the biological components. The method of administering smoke in an *in vitro* system is inadequate for

Epidemiology

It is possible to study the combustion products in a population of people. The outcome in the study designs with a control group is to the satisfaction of the investigator. The second aim is to determine which method does not cause the diseases of death. This summarises the

Table 1. Pro

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limit to the dose that can be tested due to the presence of carbon monoxide. Of course, it is possible to separate the various chemicals in smoke, and apply them to volunteers in exposure chambers, either individually, or in defined mixtures, but then it is barely possible to measure any interactions between the different components. Any reduction in the scale of the test system, for example by administering smoke to tissue cultures, still involves an extrapolation from the *in vitro* system to intact man. The experimental methods available are inadequate for this purpose.

Epidemiology

It is possible to measure the effects of long-term exposure of man to combustion products by epidemiological techniques. With this approach, a population of exposed individuals is identified and the rate of any medical outcome in this group is compared with that in a suitable control group. Two study designs are possible. First, one can either start by identifying individuals with a condition (i.e. cases) and attempt to show a greater exposure in the past to the suspected cause than occurs in a demographically matched control group. The second approach is to assemble a population (i.e. cohort) of individuals and determine what happens to them medically over several years. The cohort method does not provide rapid answers, especially with the most frequent causes of death, which frequently have a slowly developed pathology. Table 1 summarises the problems associated with such studies.

Table 1 Problems in Epidemiology

1.	Selection of exposure and control groups
2.	Multifactorial nature of disease
3.	Difficulty in controlling confounding variables
4.	Only associations detected
5.	Intervention studies are difficult

The best way to understand the difficulties of such epidemiological investigation is to examine the quality of the evidence in a specific case. As the regulators are currently considering the health effects that may result from exposure to environmental tobacco smoke (ETS), this will serve as an appropriate example. The latest claims are that ETS is causally related to ischaemic heart disease, so the quality of this evidence will be considered in detail. However, the investigator is confronted by comparable difficulties with combustion products from any fuel source.

Study Design

The study design is shown in figure 1. The exposed group are obtained by selecting non-smokers who are married to smokers, whereas non-smokers married to non-smokers provide the unexposed group. The rationale of this design is that the non-smokers (usually wives) would be exposed to ETS in the home from the smoking of their spouses. With these two populations, it is possible to compare the rates for ischaemic heart disease, either in case-control or cohort studies. The problems of interpretation arise from the imprecise distinction between the two exposure groups, and because there is no allowance made for exposure to ETS outside the home. A second difficulty is the determination of the smoking status of the spouse, which is usually achieved from the response of individuals to questionnaires. Any wrongly classified partners tends to reduce the precision of the study.

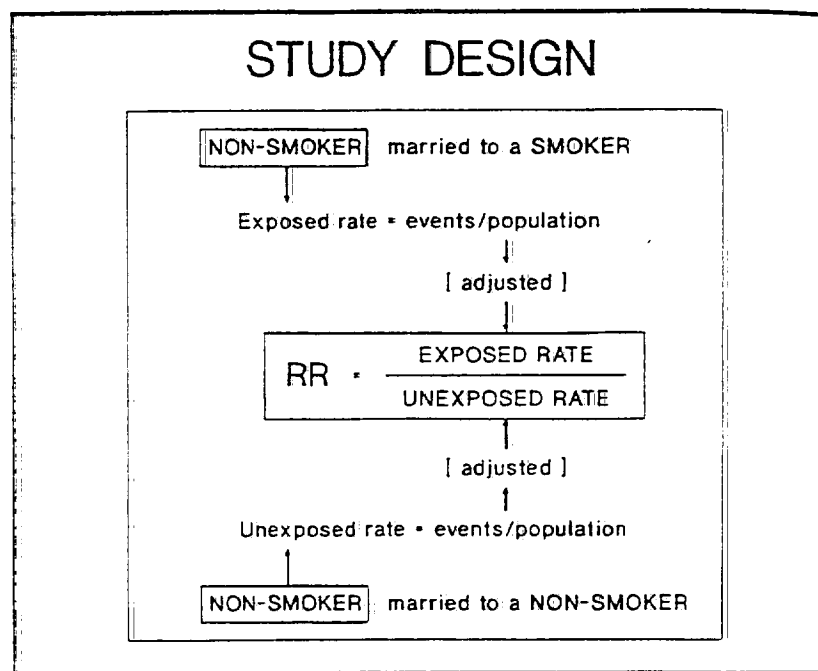


Figure 1.

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A quite different set of problems relate to the definition of an effect, i.e. those who have the disease. If one relies on death certificate information, then the fact that the individual has died is reliable, but the cause of death is prone to error [2]. As few autopsies are now performed in most countries of the world (for example, currently, less than 13% of bodies in the USA are subjected to autopsy [3]), the cause of death has to be deduced from the signs and symptoms of the patient alone.

If the possible causes of ischaemic heart disease are considered, medical scientists do not have an unequivocal answer. This has resulted in a sort of second level approach, where risk factors apparently predisposing individuals to cardiovascular disease are identified. In other words, the aetiology of cardiovascular disease is considered to be multifactorial. To date, over 200 such risk factors have been proposed by various research groups [4] (not all medical scientists agree with this approach: McCormick and Skrabanek [5] have suggested that we should refer to risk markers, as opposed to risk factors, so as not to confuse association with causation). However, if there are constitutional or behavioral characteristics of individuals that could predispose them to cardiovascular disease, each one should be controlled for in epidemiological studies, otherwise they may act as confounders, allowing an incorrect conclusion to be reached.

Much of the interest in ETS and cardiovascular disease arises from a review by Glanz and Parmley [6], in which the authors presented a case that ETS was responsible for a proportion of the cases of the disease. Nine epidemiological studies were identified in the literature (5 with a statistically significant effect, supposedly from spousal exposure [7-11]), and 4 without [12-15], which allowed Glantz and Parmley to conclude "These epidemiological studies demonstrate a connection between ETS exposure and death from heart disease." One other study [16] has been added to the ones covered by Glanz and Parmley.

Table 2 contains a summary of the epidemiological studies linking ETS with cardiovascular disease. The medical endpoint varies from study to study, and contains both "death from" and "possession of" the specified condition; the following conditions were taken as the endpoint: ischaemic heart disease, arteriosclerotic heart disease, coronary heart disease, myocardial infarction, stroke, and all cardiovascular diseases. The reliance on death certificate information as the medical endpoint is also indicated in table 2.

Table 2: The Epidemiological studies of ETS and cardiovascular diseases.

STUDY	REFERENCE	DISEASE	END POINT	TOTAL EVENTS	TESTS sig/total
BUTLER	[12]	CHD	D.C	64	0/1
HIRAYAMA	[10]	IHD	D.C.	494	1/3
GARLAND	[13]	IHD	D.C	19	0/10
LEE	[15]	IHD + STROKE	DIAGNOSIS	121	0/30
SVENDSEN	[11]	CHD	PANEL	13	2/17
HE	[8]	CHD	DIAGNOSIS	34	24/47
HELSING	[7]	AHD	D.C.	2014	10/22
HOLE	[9]	IHD	D.C + PANEL	84	1/5
HUMBLE	[14]	All CVD	D.C.	76	0/24
DOBSON	[16]	MI	D.C + PANEL	382	2/12

Under EVENTS, the numbers refer to those in the CONTROL + EXPOSED groups for the cohort studies, and the number of cases in the case-control studies, and give an indication of the ability of the tests to detect an effect. The values are for males and females combined, and both home and work place exposure to ETS.

IHD = ischaemic heart disease
 CHD = coronary heart disease
 AHD = atherosclerotic heart disease
 MI = myocardial infarction
 CVD = cardiovascular disease
 D.C. = death certificate
 PANEL = evidence reviewed by a panel of experts
 DIAGNOSIS = disease determined by standard diagnostic techniques

The large number of comparisons made in the papers is indicated in Table 2. When multiple comparisons are made on one set of data, the comparisons are not truly independent (some values will be used and then re-used in different tests), so any study containing a statistically significant outcome will be considered further. The positive studies are re-considered in Table 3.

It has already been stated that cardiovascular diseases are thought to be multifactorial in their aetiology, so any putative causes other than exposure to ETS that are not controlled for will be capable of confounding the epidemiological studies. For this reason, some of the best established risk factors for cardiovascular diseases have been identified from the literature (Table 4), and the extent of the control over these potential confounders has been determined (Table 3).

Table 3: Missing epidemiological studies.

STUDY
HIRAYAMA [10]
SVENDSEN [11]
HE [8]
HELSING [7]
HOLE [9]
DOBSON [16]

In no study was the family history of cardiovascular disease (8). The Svendsen study was a case-control study of behaviour.

Table 4: The best established risk factors for cardiovascular diseases.

RISK FACTOR
Family history of cardiovascular disease
Hypertension
Cigarette smoking
Dietary fat load
Diabetes
Lack of exercise
Menopausal status
Alcohol consumption
Obesity

From table 3 it can be seen that the same standard. Svendsen et al [11] (10 years exposure to ETS concentration). The dietary fat intake of the population selected for the U.S. population. The cardiovascular diseases were high blood pressure and those most at risk of any effect of ETS.

diseases.

TESTS sig/total
0/1
1/3
0/10
0/30
2/17
24/47
10/22
1/5
0/24
2/12

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Table 3 Missing evidence (potential confounding variables) in the positive epidemiological studies

STUDY	Obesity	Hypertension	Alcohol	Fatty Diet
HIRAYAMA [10]	NO	NO	YES	NO
SVENDSEN [11]	YES	YES	YES	YES
HE [8]	YES	YES	YES	YES
HELSING [7]	NO	NO	NO	NO
HOLE [9]	YES	YES	NO	YES
DOBSON [16]	NO	NO	NO	NO

In no study was the following controlled for: diabetes, exercise and menopausal status in women. Family history of cardiovascular disease was not controlled for, except in the study by He et al [8]. The Svendsen et al study [11] was the only one to employ a marker to detect smoking behaviour.

Table 4 The best established cardiovascular risk factors.

RISK FACTOR	SELECTED REFERENCES
Family history of disease	[18, 19, 20]
Hypertension	[21, 22]
Cigarette smoking	[17, 22]
Dietary fat load	[22, 23]
Diabetes	[18]
Lack of exercise	[24, 25]
Menopausal status	[18, 26, 27]
Alcohol consumption	[4]
Obesity	[28]

From table 3 it is apparent that the epidemiological studies are not all of the same standard. Perhaps the best designed study was that performed by Svendsen et al [11]. This was the only study that attempted to confirm the exposure to ETS by measuring a marker of exposure (serum thiocyanate concentration). The potential confounders of hypertension, body weight, dietary fat intake and alcohol consumption were all controlled for, but the population selected for study was atypical. The subjects were from the 15% of the U.S. population thought to be at greatest risk from cardiovascular disease. The cardiovascular disease risk factors considered to be important in this study were high blood pressure, cigarette smoking and high blood cholesterol levels, and those most at risk possessed two of the three risk factors. When it came to any effect of ETS, this was measured in non-smokers by the spousal smoking

status method. Thus all ETS exposed subjects must have been both hypertensive and had high blood cholesterol levels. However, 3 really important cardiovascular disease risk factors (family history of cardiovascular disease, glucose tolerance and whether or not the subjects exercised) were not controlled for. The final point that needs to be made from this well-designed study was that exposure to ETS was not associated with possession of a cardiovascular disease in a statistically significant manner: the significant result that qualifies it for examination in Table 3 was between surrogate exposure to ETS and death from all causes.

The two studies that provided the highest proportion of statistically significant associations between ETS exposure and death from cardiovascular disease were by Helsing and others [7] and by He et al [8]. The study by Helsing et al was the least well controlled of all the studies considered here. There was no attempt to confirm exposure to tobacco smoke (either from ETS or undisclosed smoking). No information was reported about blood pressure, body weight, dietary fat intake, alcohol consumption, family history of cardiovascular disease, glucose tolerance, exercise, and menopausal status of the female subjects. In fact this study is best considered to be a linking of death certificate information to the response to a self-administered questionnaire. When one considers the absence of control over potential confounders, no reliance can be placed on the findings.

The case-control study from China [8] has only been published in Chinese, but the 34 female coronary heart disease patients were shown to be at risk from spousal smoking (OR = 3.52, confidence limits, $P = 0.05$, 1.26 - 7.17). This remarkable level of risk greatly exceeds many estimates of the direct effects of smoking [9, 17]. The effects of potential confounding influences was assessed in a multivariate logistical regression analysis, where it was shown that the effects of surrogate exposure to ETS persisted when the following risk factors were controlled for: previous history of hypertension, family history of hypertension, family history of coronary heart disease, history of passive smoking, amount of exercise, and previous history of hyper-cholesterolaemia. However, this study on a small group of only 34 patients needs to be extended, evidence of the effects of direct smoking determined, and evidence of difference in diet between the cases and controls added.

The quality of the other studies considered here lie between those of Svendsen et al and Helsing et al. All are poorly controlled. A study of appropriate standard and size has not yet been performed, so it is not yet possible to decide whether or not there is an association between exposure to ETS and cardiovascular disease. The fundamental problems in study design consist of:

- a: the selection of the exposed and control groups;
- b: the exact classification of disease; and
- c: the exercise of adequate control over the numerous potential confounding variables. Much the same difficulty arises with any attempts to examine the

possible association

Table 5 To progress medical criteria: criteria:

1. The association less than 3 (29)
2. There should be
3. The effect should
4. The temporal: pathological
5. There should be more cases than
6. There should be
7. All the evidence

In virtually all cases, the more persuasive

If one were at combustion products, the case-control study cause the disease. causes the conditions properties of an causation can be amongst epidemic all cases, there is outcome is caused

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possible association between combustion products and common diseases.

Table 5 To progress from the association of an environmental factor with a medical outcome to establishing causality, several steps have to be taken. The whole of the evidence should conform to the following criteria.

1.	The association should be strong enough to be persuasive: it is seldom the case with RR less than 3 [29].
2.	There should be consistency of findings between different studies.
3.	The effect should be specific, or as near to this as possible, with the exposed group.
4.	The temporal relationship with respect to exposure should be appropriate to the pathological sequence of the disease.
5.	There should be a dose-response relationship, whereby the greater exposures result in more cases than occurs in the less exposed group of individuals.
6.	There should be a "freedom from implausibility" with respect to biological mechanisms.
7.	All the evidence should be coherent and point towards one conclusion.
In virtually all cases, the full set of criteria are not fulfilled, but the nearer one is to achieving this, the more persuasive is the argument. (Adapted from [2].)	

If one were able to show a statistically significant association between combustion products and disease in an epidemiological study, as is the case with the case-control study from China [8], it is still not evidence that the products cause the disease. Association is only association: to conclude that exposure causes the condition, further steps are needed. Table 5 indicates some of the properties of an association that would have to be demonstrated before causation can be concluded. It should be noted that there is much debate amongst epidemiologists as to the exact criteria for taking this further step. In all cases, there is an element of subjectivity in reaching the decision that the outcome is caused by the influence studied.

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CORONARY HEART DISEASE AND INVOLUNTARY SMOKING

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The coronary heart disease (CHD) is one of the major causes of death in the western world. There is general consensus on the central role of the cholesterol concentrations in blood, reflecting the levels of atherogenic lipoproteins, especially of low density lipoproteins in the development of atherosclerosis. Other risk factors for coronary heart disease like hypertension, diabetes and active smoking potentiate the risk for atherosclerosis in hypercholesterolemic patients. These additional risk factors - one leading risk factor is active smoking - enhance the coronary risk particularly in patients with only mild hypercholesterolemia (LDL-cholesterol 120-190 mg/dl). However, in severe hypercholesterolemia additional risk factors such as active smoking do not appear to aggravate coronary risk any further [1]. These findings of our follow-up study on incidence and prevalence of coronary heart disease in 6000 industrial workers are in agreement with other population studies [2, 3].

In spite of the central role of plasma lipoproteins in the development of coronary heart disease and of the risk factor 'smoking' it is also worthwhile to focus our attention on the effects of involuntary smoking and its relationship to the process of atherogenesis. Atherosclerosis can be described as a 'response to injury' of the arterial wall. The initial events causing endothelial injury may vary, but lipoproteins themselves contribute to such injury. This could be due to increased permeability of the endothelium for plasma lipoproteins, the release of growth factors and chemotactic substances. In addition hypertension, diabetes, oxidized lipoproteins,

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high plasma fibrinogen levels and plasma viscosity, active smoking and distress may be further important causes for the initial injury of the vessel wall [4, 5].

To determine whether a relationship between passive smoking and atherosclerosis exists, we should first ask for a pathobiochemical concept and experimental investigations to explain the proposed toxic effects of involuntary smoking. However, there are no experimental studies that can demonstrate a definite effect of passive smoking on the development of atherosclerosis. But there are a few epidemiological investigations on the incidence of coronary heart disease in active and passive smokers. However, all of these epidemiological investigations reveal a number of weaknesses in design and execution so that the results should be regarded with a certain amount of caution. The named deficiencies may be explained by the fact that these studies originally were aimed at investigating other issues and the results have subsequently been analyzed for an association between passive smoking and CHD.

The following deficiencies can be found in literally all population studies on passive smoking and actual CHD.

1. Active smoking could not be ruled out with certainty for all the subjects investigated who claimed to be passive smokers.
2. Passive smoking exposure was inadequately assessed, and was mostly based on secondary information about the spouse's smoking habit, while the spouse was often not questioned personally.
3. No assessment of the subjects' smoking behaviour or their passive smoke exposure was carried out during the study periods.
4. There was no clear definition of the target event (normally death from CHD) and no indication of the findings required for the target diagnosis.

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5. The influence of other risk factors generally known to be strongly associated with coronary heart disease, such as hypercholesterolemia, hypertension and psychosocial factors on the results of the studies has not been taken into account.

According to the data published by HIRAYAMA (1981) [6] the risk of death from CHD was completely identical for women exposed to passive smoking as for those who were not exposed. This analysis was based on 406 deaths from CHD in the observation period of 13 to 15 years and a total of more than 90.000 subjects investigated. What is striking is the fact that in a reanalysis of the same group carried out in 1984 [7], which was based on only 88 additional deaths, the same author found a risk, compared to non-exposed women, which was significantly increased by a factor of 1.1 for women married to ex-smokers and for women married to smokers with a daily cigarette consumption of 1-19, while women married to heavier smokers showed a risk significantly increased by 1.3 times. When we look at the change in the findings between 1981 and 1984, together with the general deficiencies mentioned above, the results of this study must be regarded as questionable.

In another study by GILLIES [8], from the total study group of 16.000 subjects approximately 1.000 non-exposed men and women were compared with about 1.700 passive smokers for the risk of death from CHD or stroke. The results were inconsistent: While in women the incidence rates for the vascular diseases stated above were slightly higher for passive smokers than for the non-exposed subjects, the incidence rates in men were higher in the non-exposed subjects than in those exposed to passive smoking. Incidence rates always differed by less than one case per 1.000 subjects and year. In view of these marginal differences and the rather low absolute number of cases, the authors did not see any point in calculating the significance level. In an update of this report by David Hole and coworkers [8], the

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authors investigated about further 8000 subjects recruited from a Westscotish population for the effects of passive smoking in relation to cardiovascular symptoms. Passive smokers were grouped in terms of high and low exposure. The high exposure group showed a large number of symptoms and an increased mortality rate in coronary heart disease by 2.01.

The fact that only 80% of the population cohort were investigated and that the study was confined to subjects between 45-60 years of age, so that only insufficient information on the smoking habits of all persons living in the household was obtained, may be regarded as a limiting factor of this investigation. Moreover, additional interviews revealed that 5% of the men and 21% of the women, categorized as controls in the study by Hole, lived indeed together with current smokers, who, however, were not included in the study. Another serious shortcoming may be seen in the relatively small number of observed deaths; consequently, confidence intervals are rather large, so that a significant difference could only be found for deaths on ischemic heart disease, with the relative risk of passive smokers of 2.01, coming close to that of active smokers by 2.27. However, the relative risk for cardiovascular symptoms in passive smokers compared with controls was not significantly different.

Garland [10] analyzed the risk of death from CHD in 695 married women who were categorized according to the spouses' smoking habits, broken down into 'never smokers', 'ex-smokers', and 'current smokers'. In women married to ex-smokers, the risk of death from CHD was found to be 3.6 times increased, while in women married to current smokers the risk was 2.7 times increased as against non-exposed women. Apart from the deficiency mentioned above, it is striking that in this study women married to ex-smokers are alledged to have a higher risk than women married to current smokers. This is hardly in keeping with epidemiological findings according to which even in active smokers after giving up smoking the risk of death from CHD shows a relatively rapid decline to the level of never smokers. Hence, there is hardly

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any pathophysiological explanation for the findings of Garland, so that the suspicion of misclassification arises. It should be added that the analysis of the study was based on only 19 deaths from CHD, so already one single case of death more or fewer in this or that subgroup of the study population could produce diametrically opposed results. Consequently, statistical significance reaches only a level of 90%, although, a 95% level is usually required.

A further study by Lee [11] is the only non-prospective and the only case control study among the investigations dealt with here. Lee did not find any relationship between passive smoking and coronary heart disease or stroke. However, it should be pointed out that this study can also not entirely be excluded from the criticism mentioned above.

As a part of the Multiple Risk Factor Intervention Trial Svendsen and coworkers [12] compared a total of 1,300 non-smoking men with either smoking or non-smoking wives, with regard to the risk of CHD and death from CHD. Again the study was based only on a small number of cases. The authors found for those exposed to passive smoke in an observation period of 6-8 years a 1.6 times increased risk of newly developed coronary heart disease and a 2.2 times increased risk of deaths from CHD. However, the differences in the coronary risk did not reach significance level. Although the study reveals certain advantages as clearly defined target events, validation of diagnosis of target events, consideration of other risk factors, and assessment of the subjects smoking habits during the study period, these are outweighed by the fact that the subjects were primarily participating in the CHD intervention study including drastic medical care to reduce the risk factors of CHD, such as a dietary advice or antihypertensive medication. This led to a large number of confounding factors likely to affect the results of the study. A particular weakness is the fact that the study also failed to assess the spouses' smoking habits, especially the extent of tobacco smoke exposure during the study period.

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Finally, Sandler and coworkers [13] studied the frequency of deaths from CHD in passive smokers by estimating the degree of exposure on the basis of the smoker anamneses of all persons living with the subjects in the same households. The author compared CHD death rates in these passive smokers with those in non-exposed subjects and found a 1.2 to 1.3 times elevated risk, with the increase just reaching significance, during the 12 year period of follow-up. A dose-effect relationship could, however, not be demonstrated. Furthermore, the critical points mentioned above apply to this study as well. There was no assessment of passive smoke exposure during the period of follow-up and it is unlikely that all persons in a household would maintain the same smoking behaviour over a period of 12 years. The authors themselves have considerable reservation on this point.

Taking into account the small increase in coronary risk in passive smokers as compared to non-exposed subjects and also the low validity and small number of epidemiological studies available and the fact that their results are at least inconsistent, a relationship between passive smoking and cardiovascular diseases cannot be established on these data.

The American Surgeon General, in his report from 1986 arrives to the same conclusion by stating [14]:

'The magnitude of risk associated with involuntary smoking exposure is uncertain. Sample sizes in most studies are not large, the point estimates of effect are unstable, and confidence limits are broad and generally overlap from one study to another.'

It should be added that the current epidemiological methods seem to be not sensitive enough to reveal a relationship between passive smoking and CHD, and to distinguish it from the effects of major risk factors, such as hypercholesterolemia.

Furthermore, a review by the National Research Council [15] estimated

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that the relative risk of coronary heart disease in nonsmokers exposed to environmental tobacco smoke as compared with that in true nonsmokers would be approximately 1.02 - an increment difficult to detect or estimate reliably in nonexperimental studies.

The question arises, whether evidence can be provided on a pathophysiological basis, pointing to a role of passive smoking in the development of cardiovascular diseases. It has widely been accepted that it is primarily nicotine and carbon monoxide which may account for an increased tendency towards atherosclerotic changes of the arterial wall in active smokers. However, it has been demonstrated that under normal life conditions the blood levels for carbon monoxide, nicotine and cotinine measured in passive smokers hardly differ from those found in non-exposed subjects at all, whereas smokers show concentrations of these substances which are many times higher as compared to the controls [16, 17]. Several active mechanisms are in discussion, at least for nicotine, by which the substance may contribute to the development of atherosclerosis [18]. However, in view of these low concentrations, it can be ruled out as an important factor for an elevated risk of CHD to passive smoking.

If therefore nicotine and carbon monoxide cannot be made responsible for an assumed elevated risk of CHD in passive smokers, which of the substances will then account for this as toxic agent?

So far there are no well-documented relevant findings from appropriate experiments or epidemiological studies whatsoever. However, one further experimental consideration could be the determination of chemically modified lipoproteins and the investigation of the oxidation of lipoprotein particles in the plasma of passive smoking subjects. Modified lipoproteins have been found to be present in atherosclerotic plaques and products of oxidation have been seen in early and late lesions [19]. There is increasing evidence that oxidized lipoproteins may play an important role in atherogenesis. It has been shown that oxidized LDL enhances monocyte-endothelial

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interactions and can accumulate in macrophages [20]. Previous studies could demonstrate that oxidation of lipoproteins in plasma derived from smokers is facilitated compared to non-smoking controls. However, it can be expected that the concentration of inhaled oxidizing substances and free radicals during passive smoking will be very low.

In conclusion it should be pointed out that on the basis of published studies and data available a relationship between passive smoking and coronary heart disease cannot be established. In contrast to these inconsistent observations, it is a matter of fact, that a primary and secondary prevention of coronary heart disease is possible by changing life habits including a change of nutritional habits, normalizing hypercholesterolemia and high blood pressure and to stop active smoking [21, 22, 23].

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OTHER PEOPLE'S TOBACCO SMOKE

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7. Environmental Tobacco Smoke and Coronary Heart Disease

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1. What is coronary heart disease?

Before considering whether exposure of the non-smoker to ETS represents a health risk, let us highlight, briefly and simply, some of the basic physiology, anatomy and pathology of importance to an understanding of coronary heart disease (CHD). This type of heart disease, also known as ischaemic heart disease, has been at the centre of public health interest for 25 years because it is the leading cause of death in many countries, including the UK and the USA.

The heart is a blood-filled bag of muscle, which contracts and relaxes roughly 70 times a minute to pump blood around the body. It has a remarkable capacity to adapt its performance throughout life, according to the needs of the body, by varying its rate and strength of beat. As one of the most active tissues in the body, the heart muscle needs a good supply of oxygen to function efficiently. This supply is not obtained from the blood which is pumped through the chambers of the heart, but from blood pumped through the coronary arteries. These arteries branch off from the main artery (aorta) as it leaves the heart and they then divide into a network of smaller branches which fan out all over the surface of the heart.

Over a period of many years, the walls of the coronary arteries gradually 'fur up' with fatty deposits known as atheroma. This condition, when severe, is coronary heart disease, the clinical manifestations of which appear in two forms — angina and heart attack. If the narrowing of the coronary arteries is very gradual (as it usually is) then the first sign of trouble may only be noticed when the heart has to work harder than usual. For example, during brisk exercise, the heart muscle may fail to receive an adequate supply of oxygenated blood and chest pains (angina) may result. The symptoms are generally relieved by resting for a few minutes. A heart

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attack, on the other hand, occurs when there is a sudden and severe blockage of one of the coronary arteries, so that the blood supply to part of the heart muscle is not merely reduced, but cut off. The blockage is usually caused by a blood clot forming in an artery already severely affected by fatty atheroma and is known as a coronary thrombosis. The part of the heart muscle affected is severely damaged (myocardial infarction) causing the *prolonged* pain that is the most common symptom of a heart attack. Sometimes the blockage is so severe that the heart stops beating in a coordinated manner and circulation of blood to all the tissues of the body effectively stops. Unless the heart starts beating normally within a few minutes, the person will die.

2. What causes coronary heart disease?

Death rates from CHD vary widely from country to country. For example, in 1984 the figures for the age group 55-64 were in excess of 800 per 100,000 in Northern Ireland, Scotland and Finland and less than 100 per 100,000 in Japan. Research workers are still trying to discover exactly what it is in our everyday lives that increases the risk of heart attack and angina. It seems certain that there is no single cause; the major risk factors are usually said to be high blood pressure, high levels of cholesterol in the blood and cigarette smoking. In addition, diabetes, lack of exercise and a generally aggressive work temperament (so-called Type A behaviour) are all considered to contribute to the multifactorial atherogenic process (Kannel, 1981).

3. Active cigarette smoking and coronary heart disease

It has been reported that male cigarette smokers, but not pipe and cigar smokers, have consistently higher overall death rates than non-smokers from CHD in many, but not all, Western societies. The size of the risk is claimed to be dependent on age and daily consumption of cigarettes, being greater in men under 50 years of age than in older men. The various epidemiology studies consider mortality ratios in slightly different age ranges. For men aged 'around 50', the reported mortality ratios are some 2-3 times greater than those of non-smokers. In men aged 60 and above, however, when death from heart attacks is in any case more prevalent, the mortality ratios are consistently lower, around 1.5 (Surgeon General's Report, 1983). In female smokers, the reported association between cigarette smoking and CHD is much weaker. Several studies indicate that cigarette smoking may occasionally precipitate anginal pain in some patients or reduce exercise tolerance in others. In others, the frequency and severity of atheroma of the coronary arteries at *post mortem* were greater in smokers than in non-smokers. (For specific references, see Royal College of Physicians, Reports 1-4, on Smoking and Health, 1962, 1971, 1977, 1983.)

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On an acute basis, the act of cigarette smoking causes a marked increase in heart rate, an increase in cardiac output and a relatively smaller increase in blood pressure. The effects are due to absorption of nicotine into the bloodstream, increase with degree of inhalation, and in *healthy* subjects are perfectly *normal* and *harmless*. In subjects who have already had a heart attack and suffered a myocardial infarction, however, a fall in cardiac output may occur. It follows that such subjects who can readily be identified should not smoke cigarettes (Pentecost and Shillingford, 1964).

Although the public health lobby frequently claims a causal relationship between active cigarette smoking and CHD it should not be forgotten that the disease is a common affliction among non-smokers. Furthermore, there is much evidence that is not wholly consistent with a claim of causation (Seltzer, 1980, 1981). One notable objection is lack of proof of the mechanisms by which cigarette smoking may accelerate development of CHD and precipitate death. Nicotine and carbon monoxide have been implicated at one time or another, but the reasons have been theoretical and emotional, rather than strictly factual.

The possibilities have been fully discussed by Wynder *et al.* (1976), while Cohen and Roe (1981) elegantly summarised the actions of nicotine that might play a role in cardiovascular disease. In the opinion of the present author, however, it is misleading to state that cigarette smoking, nicotine and carbon monoxide may cause CHD. A similar claim for eating is just as reasonable! After all, our restricted diet in World War II and for the rest of the 1940s had a favourable effect on CHD death statistics.

4. ETS and coronary heart disease

The foregoing summary concerning active cigarette smoking and CHD provides the basis for comparing the role of ETS. On this subject, there are relatively few relevant published data, which is reflected in the fact that cardiovascular diseases occupied only two of the 359 pages of the recent Surgeon General's report, *The Health Consequences of Involuntary Smoking* (1986), and did not feature in any of the 16 paragraphs concerned with exposure to ETS of the 4th Report of the Independent Committee on Smoking and Health (1988).

5. Dosimetry

The concentration of ETS to which an individual is exposed depends on:

- Type and number of cigarettes burned
- Volume of room
- Ventilation rate
- Proximity of burning cigarette

The effective dose for an exposed individual is the dynamic integration of concentration in various environments and the time the individual spends in

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these environments. These considerations highlight the difficulty of assessing accurate dosage under 'real life' conditions, which is one major weakness of most, if not all, ETS epidemiology studies. It is possible to measure the concentration of specific components in ETS, and the two most common marker substances are nicotine and carbon monoxide. In a recent study (Kirk *et al.*, 1988), large differences were shown to exist according to the environmental circumstances — for example, travel, leisure, work, home. The concentration of nicotine varied from non-detectable to a maximum of the order of 400 micrograms per cubic metre (mean approximately 15 micrograms per cubic metre); for carbon monoxide the range was 0-30 parts per million with a mean concentration of around 2.5 parts per million. With an individual exposed to ETS, there is normal breathing of diluted sidestream smoke (SS) and exhaled mainstream smoke (MS) from active smokers. This contrasts with the situation obtaining for the active cigarette smoker, who takes a puff of neat smoke into the mouth and then inhales it. Under these circumstances, the concentration of nicotine and carbon monoxide to which the alveolar membranes of the lung are exposed is of a totally different order of magnitude — perhaps as much as 1000 times. On theoretical consideration, therefore, the dice are heavily loaded against significant absorption of nicotine and carbon monoxide, and indeed any other putative cardiovascular toxins like nitrogen dioxide.

The theory is borne out in practice because cotinine levels in blood, saliva and urine, which are often used as a measurement of nicotine absorption of non-smokers exposed to ETS, are approximately 1% of those measured in active smokers (Jarvis *et al.*, 1984). Blood carboxyhaemoglobin levels (COHb) have been measured in non-smokers exposed to ETS under real life and artificially exaggerated conditions. They were generally in the range 1-1.5% under realistic exposure conditions.

6. Effect of ETS exposure on heart rate of healthy subjects

Normal healthy subjects exposed to ETS for periods up to two hours under resting or exercise conditions have been studied. There were no significant changes in heart rate or blood pressure in adult men and women, indicative of the absorption of negligible amounts of nicotine (National Research Council, 1986).

7. Effect of ETS exposure on heart rate of angina patients

Various studies, conducted mainly by Aronow and colleagues, have demonstrated that exercise-induced angina develops more rapidly in patients diagnosed with classic stable angina pectoris exposed to 50 parts per million carbon monoxide for periods from 1-4 hours. These concentrations are on the high side compared with those measured by Kirk *et al.* (1988) and measured levels of COHb were in fact in the range 2-4%. Only one

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experiment on the effects of ETS exposure has been reported (Aronow, 1978) in which 10 patients were exposed to other people's smoke (15 cigarettes) in a small room during two hours. Even under good conditions of ventilation, when the mean carboxyhaemoglobin level was only 1.77%, there was an apparent substantial reduction in the duration of exercise until the onset of pain. The results of this experiment are questionable because the study was not conducted on a strict double blind basis, the measured end point was a subjective one, and furthermore, the validity of Aronow's work has been critically questioned (Budiansky, 1983).

8. Chronic effects of ETS exposure

Because of the many factors that play a role in the development of fatal CHD, epidemiology studies need to be carefully designed and, in addition, need to use elaborate, and appropriate, statistical techniques if they are to provide unequivocal results. This is particularly true of studies concerned with effects of ETS on non-smokers, where, based on dosimetry considerations which have already been discussed, any effects might be expected to be small. Last, but not least, the question of misclassification of smoking status, to which detailed reference has been made in the lung

Table 1 ETS and CHD — Epidemiology Studies

Author	Subjects	Major Disease Interest	Adverse effect on CHD	All risk factors adequately covered
Gillis <i>et al.</i> (1984)	Non-smoking women	Lung cancer	Yes, but sample size was small	No
Hirayama (1984,1985)	Non-smoking women	Lung cancer	Yes, relative risk 1.3 for husbands smoking more than 19 cigarettes/day	No
Garland <i>et al.</i> (1985)	Non-smoking women	CHD	Yes, but questionable statistically	No
Svensen (1985)	Non-smoking men	CHD	NS	? not much information given
Lee <i>et al.</i> (1986)	Non-smoking women	Various	No	Yes

NS = not significant

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cancer chapter, has not been considered in any CHD/ETS study apart from the case control study of Lee *et al.* (1986). This factor is as relevant to CHD as it is to lung cancer.

Rather than record the detailed numerical findings of the various studies that have been conducted, I will summarise the authors' conclusions (Table 1).

It is clear that the evidence for a harmful effect of ETS in enhancing CHD risk in non-smokers is not very convincing, as the US National Research Council also concluded in the following statement:

'With respect to chronic cardiovascular morbidity and mortality, although biologically plausible, there is no evidence of statistically significant effects due to ETS exposure, apart from the study of Hirayama in Japan.'

There are now, however, two reasons to cast doubt on the Hirayama data. Misclassification of smoking status almost certainly accentuates the apparent risk, even if it does not altogether explain it. Secondly, when he reported on the first 14 years of his prospective study in 1981, there was no mention of a higher mortality rate from CHD of non-smoking women married to smokers. It is difficult to believe that a previously unsuspected risk could become apparent merely as a consequence of 3 more years of follow-up. Any author is entitled to his opinions, but in the public health area there is a danger that if such opinions are reiterated sufficiently often, they may ultimately become accepted as facts. Lee *et al.* (1986), having considered all the available evidence, concluded that any effect of ETS exposure on risk of any of the major diseases that have been associated with active smoking is at most small, and may not exist. The case for exposure to ETS carrying any increased risk of death from CHD is the weakest of all. It has already been pointed out that in many studies the association between active cigarette smoking and CHD is much weaker in female smokers than in male smokers, or even non-existent. If an effect of smoking on the development of CHD cannot be convincingly demonstrated in female active smokers, it is difficult to assume that such an effect is possible in females exposed to ETS (Schievelbein and Richter, 1984) unless there is something particularly noxious in ETS, about which we are currently unaware. This seems unlikely.

At a recent meeting in Montreal, Wexler (1990) and a discussion panel also concluded that currently there is no clear demonstration of any increased risk of cardiovascular disease from exposure to ETS.

There is another and independent piece of evidence that casts doubt on any significant role of ETS in the development of CHD. Pipe smokers inhale tobacco smoke both actively, to a limited extent, and passively. They commonly surround themselves in a cloud of tobacco smoke, so that they are probably exposed to the highest concentrations of ETS of any group. Yet they enjoy relative immunity from the three major diseases which have

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been associated with active smoking. In conclusion, therefore, non-smokers would be much better advised to watch their weight, diet and blood pressure than to worry about any long-term harmful cardiovascular effects of exposure to ETS!

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ENVIRONMENTAL TOBACCO SMOKE AND CORONARY HEART DISEASE

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Abstract

The possibility that exposure to environmental tobacco smoke (ETS) may increase the risk of non-smokers developing coronary heart disease (CHD) is a matter of debate. The results of published epidemiology studies have been considered according to the classical criteria for judgment of causality. Twelve epidemiological studies have been published on the alleged relationship between exposure to ETS and the risk of CHD in non-smokers. The relative risks generally fall between 1 and 2, which represents a 'weak association'. Although the reported association shows some signs of consistency, it is not strong, nor it is specific. The lack of consistency between dosimetry and epidemiology casts doubt on the biological plausibility; further claims of a dose/response relationship, which are based entirely on reported cigarette usage, are not wholly convincing. On current evidence a causal relationship between exposure to ETS and the development of CHD has not been proved.

Key words: Environmental tobacco smoke (ETS), coronary heart disease (CHD), association and causality, dosimetry, publication bias, biological plausibility

Introduction

The debate regarding the association between smoking and cardiovascular diseases, especially coronary heart disease (CHD) has, during recent years, led to consideration of the possibility that exposure of non-smokers to environmental tobacco smoke (ETS) might increase the risk of such disease. The uncertainty about the existence of such an association is evident from the pronouncements of groups of scientists who carefully and critically reviewed the relevant data available at the time of their review.

1986: *US Surgeon General* [1] – "Further studies on the relationship between involuntary smoking and cardiovascular disease are needed in order to determine whether involuntary smoking increases the risk of cardiovascular disease". This view was

based on four studies which had been published at that time.

1986: *National Research Council* [2] – "With respect to chronic cardiovascular morbidity and mortality, although biologically plausible, there is no evidence of statistically significant effects due to ETS exposure, apart from the study of Hirayama in Japan" (four studies considered, three of which were also considered by the US Surgeon General).

1990: *Environmental Tobacco Smoke – Proceedings of the International Symposium at McGill University, Montreal* [3] – Dr Wexler and discussants unanimously concluded that the data from seven studies would not provide any basis for altering the Surgeon General's and the National Research Council's conclusions concerning ETS and cardiovascular disease.

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1990: *Links between passive smoking and disease: a best-evidence synthesis* [4] – This report of an 11-member working group on passive smoking stated in 1990 that “after an initial review of the literature, we determined that insufficient studies of high quality had been done in the area of cardiovascular disease to warrant comment in our review at the present time”.

Most of the studies upon which these opinions were based were not designed specifically to investigate the effects of ETS exposure on CHD. According to Weetman & Munby [5] they were later adapted to this purpose after the initial claims that ETS affected health adversely had appeared in 1981–1982. Thus, neither of the two large prospective studies [6,7] was conducted according to accepted principles, i.e. systematic collection of risk factor data at intervals and complete follow-up of all deaths. With the exception of the recent study of Dobson and associates [8], it is notable that all the other published studies involved only very small numbers of deaths [9].

Epidemiology data and the question of causality

Twelve epidemiology studies have now been published ([6–8,10–20] – see Table 1) on which to base a judgement but few details were provided for two of the case-control studies and the studies of Martin *et al.* [11], Palmer *et al.* [13] and Butler [19] have only been published as abstracts; full papers are still awaited. Some of the data in the Table are based on figures quoted by Lee [21] and Giantz & Parmley [22]. In attempting to interpret the results of these studies it is appropriate to recall the elements of evidence laid down by the United States Surgeon General [23] and the late Sir Austin Bradford Hill [24] that need to be considered before a reasonable inference of causation for studies that purport to show association can be made. Hill's elements were as follows:

- an association should be strong
- it should be consistent across a variety of subjects and circumstances
- it should be specific

- exposure must precede the observed outcome
- there should be a dose-response relationship
- the association should be biologically plausible
- evidence from all relevant scientific disciplines should be coherent
- experimental evidence should be sought whenever possible
- analogy to similar cause and effect relationships should be considered.

Hill's criteria did not actually include – “sources of bias must be excluded” – though it is implicit in the condition – “an association should be strong”. Sources of bias and confounders, which feature so prominently in all papers concerned with the association of ETS and the development of disease are, therefore, logically considered under strength of association.

The United States Surgeon General [23] wisely commented in 1964 that “Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgement which goes beyond any statement of statistical probability”. It is regrettable, however, that three decades on judgements tend to get clouded to fit in with beliefs. Each of Hill's elements will be considered in turn.

Strength of association

The possibility of an association between CHD and alleged exposure to ETS has arisen from observational studies (prospective and retrospective) of groups considered to be either exposed or not exposed to ETS. Risk of death from CHD in the exposed group relative to the unexposed group is calculated by application of appropriate statistical techniques.

There are considerable difficulties in conducting and interpreting epidemiology studies when the ‘increased risk’ is small. Indeed, it has been stated [25–28] that epidemiology cannot usually reliably predict relative risks of less than two.

Table 1. Epidemiological studies of environmental tobacco smoke (ETS) and coronary heart disease (CHD).

Reference	Location	Sex	CHD deaths or cases		Relative risk	95% conf. limits	Factors adjusted for
			Unexposed	Exposed			
Case control studies:							
Lee et al. [10]	UK	M	26	15	1.34	0.64–2.80	None
		F	22	55	.97	0.56–1.69	
Martin et al. [11]	US	F		23'	2.6	1.2–5.7	Not known
He [12]	China	F	9	25	1.5	Unknown	Age, race, residence, occupation, hypertension, family history of hypertension or CHD, alcohol, exercise, hypercholesterolaemia
Palmer et al. [13]	USA	F		7'	1.2	Unknown	Not known
Dobson et al. [8]	Australia	M	161	22	0.97	0.50–1.86	Age and history of myocardial infarction
		F	117	43	2.46	1.47–4.13	
Prospective studies:							
*Hole et al. [15]	UK	M+ F	30	54	2.01	1.21–3.35	Age, sex, class, blood pressure, cholesterol, body mass
Svensen et al. [16]	US	M	8	5	2.23	0.72–6.92	Age, blood pressure, cholesterol, weight, education, drinks
**Helsing et al. [6]	US	M	248	122	1.31	1.05–1.64	Age, marital status, schooling, housing
		F	437	551	1.19	1.04–1.36	
Hirayama [7]	Japan	F	118	376	1.15	0.94–1.42	Age
Garland et al. [17]	US	F	2	17	2.7	0.90–13.6	Age
Humble et al. [18]	US	F		76'	1.59	0.99–2.57	Age, cholesterol, blood pressure, body mass
Butler [19]	US	F		64'	1.4	0.50–3.80	Age

* Hole et al. is an update of Gillis et al. [14], but is not a separate study

**Helsing data extracted from later paper by Sandler et al. [20]

¹= total number of cases

The 12 studies provided 15 different estimates of relative risk for either men or women, and 95% confidence intervals are available for all but two of these. Table 1 shows that 13 out of 15 indicate a relative risk of >1 but eight of these have a lower confidence limit of <1 , indicative of a non-significant effect. Although the studies suggest an association, because most of the claimed relative risks lie between one and two, Hill's criterion of strength is not satisfied.

The studies by Butler [19], Dobson *et al.* [8] and Svendsen *et al.* [16] give some data on ETS exposure at home, work, leisure and travel situations. None of these supplementary results was statistically significant.

Meta-analysis

Recently the results of all studies have been combined using the technique of meta-analysis [29,22]. Wells [29], using studies available in 1987, computed a pooled relative risk of 1.3 (95% confidence interval, 1.1–1.6) for men and 1.2 (95% confidence interval, 1.1–1.4) for women. Glantz & Parmley [22] reported a relative risk of 1.3 (95% confidence interval, 1.2–1.4) for men and women combined.

Meta-analysis is a mathematical technique primarily developed for handling data from multi-centre randomised clinical trials where the same protocol for the selection of patients, the selection of control subjects, dosing and observation is followed in each of the collaborating centres. Whether such techniques are scientifically appropriate for epidemiological studies conducted in different countries by investigators using widely different methods and criteria is doubtful [30–34].

Meta-analysis does not increase the strength of the association, although by reason of narrowing the 95% confidence intervals it may produce a mathematically, though not necessarily biologically, significant relative risk. The Glantz and Parmley paper [22] has recently aroused criticism and debate [35–38] on a number of issues including the mathematical model used by Wells [29].

Misclassification bias

According to Lee [39,40] most, if not all, of the apparently higher risk of lung cancer among non-smoking women married to smokers compared to non-smoking women married to non-smokers can be explained by a bias introduced when smoking (or ex-smoking) women claim untruthfully to be non-smokers. Such misclassification leads not only to imprecision but to bias, because smokers tend to marry smokers and non-smokers tend to marry non-smokers more than would be expected by chance. Misclassification bias of this kind affects not only the interpretation of data relevant to lung cancer risk from ETS but also to some extent that relevant to CHD risk [21]. The matter of smoking habit concordance has been fully discussed by Lee [21].

Publication bias

Lee [21] has shown that there is a tendency for the studies with small numbers of deaths or cases to have the largest relative risk estimates. For example, Table 1 shows that the highest relative risk reported, i.e. 2.7 by Garland *et al.* [17] was based on only 19 deaths, whereas one of the lowest relative risks (1.19) reported by Helsing [6] was based on 1,358 deaths in the largest of the 12 studies. Lee [21] suggests that this is a manifestation of publication bias. He also points out that the American Cancer Society has relevant data on many thousands of deaths from heart disease among women who have never smoked, but has not so far reported results which, according to Lee, suggests that no relationship with ETS was found. The possibility of publication bias has been strengthened by the paper of Easterbrook *et al.* [41] which states, "we have confirmed the presence of a systematic selection bias in the publication process according to study results. Studies with a statistically significant result for the main outcome of interest were more likely to be submitted for publication and more likely to be published than studies with null results, after adjustment for confounding factors". Thus, conclusions of meta-analyses based only on published work may produce a misleading high estimate of relative risk.

Other potential confounders

Neither of the two large studies [6,7] recorded details of major risk factors for CHD such as blood pressure, blood cholesterol levels, obesity, etc, an omission criticised by a number of reviewers [3,5,21]. In the studies by Helsing/Sandler [6,20] and by Hole [15] the index of ETS exposure was based on living with a smoker, but no adjustment was made for the number of people in the household. Since household size may correlate with various facets of disease, adjustment should have been made for it in the analysis. Dobson *et al.* [8] collected data on smoking behaviour for cases and controls by different methods and showed that, for the controls, smoking frequency varied according to the location of data collection. This provides a further important example of potential bias.

Consistency of association

Statistically, assuming no systematic bias, it would appear unlikely that 13 out of 15 estimates of relative risk >1 could have arisen by chance. Although some element of consistency amongst the published studies is indicated the possibility of publication bias may have accentuated the consistency of the association.

Specificity of association

There are two distinct aspects of specificity—one relating to the exposure and one to the disease. CHD is a common cause of death in non-smokers, which is hardly surprising when almost 300 so-called risk factors have been described [42] and the literature on such risk factors "seems to expand at almost exponential rates" [43]. For this reason, the cause of CHD is frequently stated to be multifactorial in origin. It has been said that "the phrase is a synonym for 'unknown' and thus a euphemism for ignorance" [44]. CHD is of course not the only disease to be linked with ETS. There is, therefore, an absence of specificity in the association, as Wexler [3] also concluded.

Temporality

Hill [24] stressed the need to consider the temporal relationship of any association,

particularly for diseases of slow development. There are no data available on which to address the importance of the temporality of the association between ETS and CHD. In view of the multi-factorial nature of the disease, which inevitably complicates its precise development, it is doubtful if there ever will be any unequivocal data in this context.

Dose/response relationship

Exposure

ETS is a mixture of sidestream tobacco smoke (the smoke that originates from the smouldering end of a cigarette, cigar or a pipe between puffs), waste mainstream smoke (i.e. that expelled prior to inhalation) and exhaled mainstream smoke diluted with variable but much larger volumes of ambient air. Additional physical and chemical changes occur as the mixture ages. The concentration and nature of ETS to which an individual is exposed depends, among other things, on:

- type and number of cigarettes smoked in a given time
- volume of room
- ventilation rate
- proximity of burning cigarette.

The effective daily dose for any exposed individual depends upon the concentration in various environments and the time spent in these environments, which highlights the difficulty of assessing exposure under 'real life' conditions [45]. Additionally, exposure must relate to a time-span that is appropriate to the development of the disease.

ETS is a complex mix of many components and, because no known substance is representative of all of these, it is not possible to monitor ETS exposure meaningfully [5]. Nicotine comes closest to fulfilling some of the requirements for a suitable marker [46]. Kirk *et al.* [47] measured atmospheric nicotine, carbon monoxide and particulate matter in nearly 3,000 locations over 30 minute periods in travel, work, home and leisure situations. Their data show that levels vary greatly both within, and between, situations. They illustrate how inadequate and misleading is

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an assessment of ETS exposure in epidemiology studies based merely on reported smoking habits of couples living together, determined from questionnaires.

The reliability of questionnaires represents a weakness of all experimental designs, particularly when smoking spouses themselves were not always questioned [48]. Additionally, some are untruthful about their smoking status and misclassification of non-smokers who are really smokers invariably results [39,40]. In the large Helsing study [6], the only smoking data that were collected on every person was in 1963, and no attempt was made to see whether changes in smoking habits occurred during the study.

Dosimetry

Dosimetry assessment involves the measurement of a substance in biological fluids. If ETS has any affect whatsoever on CHD then the only reasonable way that this could come about is by absorption of a component or components of ETS into the systemic circulation. No such measurements have been incorporated in any epidemiological study.

As with markers of exposure, there is no single substance that is reliably representative of ETS. Both nicotine and carbon monoxide have been implicated in possible mechanisms by which active cigarette smoking may accelerate the development of CHD [49]. Nicotine and its metabolite cotinine, which has a half-life of 15–20 hours, have been measured in: (a) ETS exposed non-smokers, (b) non-smokers not exposed to ETS, (c) active smokers [50]. Very small amounts of cotinine are found in the plasma, saliva and urine of non-smokers. Whilst non-smokers allegedly exposed to ETS are reported to have higher cotinine levels than non-smokers not exposed, these levels are minute compared with those found in active smokers (about 1/300) and variation between subjects is large (up to 10-fold).

In non-smokers, endogenous production of carbon monoxide results in low blood levels of carboxyhaemoglobin (COHb) in the range 0.5–1.5% [51]. Small increases of COHb due to ETS exposure may be

indistinguishable from those due to endogenous production and non-tobacco related sources [1].

Clearly, the amounts of nicotine and carbon monoxide absorbed from ETS are small and it is unlikely that either compound plays any role in the alleged increased relative risk for CHD of non-smokers exposed to ETS. It would be surprising if any other smoke component was absorbed in significant amounts from ETS.

Dose/response

Some authors [7,12,15,16] of the studies listed in Table 1 claim that their data demonstrate a dose-response relationship between ETS exposure (based on the number of cigarettes smoked by the active smoking partner) and death from CHD. In view of the imprecision of such dosage assessment, these claims should be viewed with caution [52].

Biological plausibility

Although ETS is a different entity from mainstream smoke, it contains many of the same components, and attempts have been made to equate ETS exposure with active smoking in terms of 'cigarette equivalents'. On such exposure/dosimetry considerations, the relative risks of more than two reported in some ETS studies [8,11,15,16,17] are implausibly high, set against the reported relative risk for active smoking of 1.9 in males and 1.8 in females [53]. Professor Wald concedes that the association seems "surprisingly large" and requires explanation [54] and has commented that the risk of 1.3 given by Glantz & Parmley [22] is "too high to be biologically plausible" [55].

That one author [17] can incorrectly report a relative risk of 14.9 (the major finding of the study) and then subsequently 'correct' it to 2.7 whilst maintaining that this "does not affect the conclusions" [56], casts grave doubt on the conduct of the whole study. Likewise, when Hirayama [57] reported on the first 14 years of his prospective study, there was no mention of a higher mortality rate from CHD of non-smoking women married to smokers. Armitage [45] pointed out that "it is difficult to believe that a

previously unsuspected risk could become apparent merely as a consequence of three more years of follow-up". Doll [58] has commented that if you find something unexpected but of social significance you have a responsibility to be sure that you are right before you publicise your results to the world. In the same paper he also offered additional advice that "... as a research worker, you always ought to try to disprove your own findings".

Pipe smoking

Pipe smokers inhale tobacco smoke both actively (to an extent) and passively. They surround themselves in dense clouds of tobacco smoke and are regularly exposed to high concentrations of ETS, yet experience "little if any excess risk of death from coronary heart disease" [59]. It is unlikely that the chemical composition of pipe sidestream smoke would differ appreciably from that of cigarette sidestream smoke. Therefore, these observations provide suggestive evidence against a role of ETS as a cause of death from CHD.

Coherence

This criterion addresses the effects of ETS on biological systems which have been claimed to support a causative hypothesis.

Platelet function

Glantz & Parmley [22] claimed that ETS adversely affects platelet function in a way that increases the risk of heart disease. This conclusion is not warranted considering that the study cited [60] measured a response to an ETS insult in non-smokers kept together in an 18m² room for 20 minutes, while testers smoked "30 heavy brand" cigarettes. The relevance of these 'artificial' experiments to CHD problems is questionable. It is not known whether, under normal conditions of ETS exposure encountered in real-life situations, the platelet function of non-smokers exposed to ETS differs from the platelet function of non-smokers not so exposed.

Fibrinogen levels and thrombogenesis

Dobson and associates [8] reported plasma fibrinogen concentrations in the control

subjects of their case-control study in an attempt to provide mechanistic support to their conclusion that exposure to ETS in the home increases the risk of fatal and non-fatal heart attack. The authors state that "people exposed to passive smoking had higher levels than those not exposed (except for passive smoking at home for women)". However, the results were not significant and the workplace means for non-smoking men and women (exposed vs. non-exposed) were virtually the same.

Effects of ETS/carbon monoxide on exercise tolerance

Healthy people can inhale enough carbon monoxide to reduce the oxygen carrying capacity of the blood by 10% or more, without ill-effect [61]. However, people with reduced circulatory efficiency (e.g. because of existing heart disease) may be temporarily compromised by exposure to carbon monoxide; their exercise tolerance may be reduced and they may develop anginal pain sooner than in the absence of carbon monoxide. Aronow [62] reported a reduction in the duration of exercise until the onset of pain in 10 patients exposed to ETS, which resulted in mean COHb levels of 1.77% and concluded that exposure to ETS was harmful to patients with angina pectoris. Aronow's experiments were not conducted on a strict double-blind basis and the measured end-point was a subjective one. Much of his work has now been generally discredited [1,63,64]. Sheps *et al.* [65] have since shown that blood levels as high as 4% COHb have no significant effect on a range of parameters examined in patients with ischaemic heart disease. This well-controlled study casts considerable doubt on the suggestion that elevation of carbon monoxide levels in the blood resulting from ETS exposure is demonstrably harmful.

Experiment

Hill [24] asked whether the frequency of the associated event (CHD death) was affected by preventative action (modifying ETS exposure). No data relevant to this question are currently available. Whether it would be possible to design a sufficiently sensitive

study to demonstrate objectively the value of preventative action in any specific situation seems questionable.

Analogy

ETS is one of the many problematical materials on which toxicologists have had to make safety evaluation judgements because of its variable composition and complex physico-chemical properties. The obvious analogy is with mainstream tobacco smoke to which reference has been made in the section on biological plausibility. Great caution, however, needs to be exercised in making judgements in this context [52].

Conclusion

The case for ETS exposure causing CHD is wholly unconvincing because almost all of the accepted 'causational' criteria remain unsatisfied. Of particular concern is the weakness of the association, the likelihood of the existence of publication bias resulting in an overestimate of a very low relative risk, the lack of biological plausibility and the anecdotal nature of dosimetry assessment.

At the present time, therefore, one is not able to conclude categorically that ETS is, or is not, harmful in a cardiovascular context. It is debatable whether the conduct of further epidemiological studies, frequently recommended, is practical and justified. Small studies are a waste of time and money because at best they can only detect large risks as significant. Of course it is *theoretically* possible to conduct a prospective study, as envisaged by Wexler [3], which would control for all confounding variables and involve a sufficient number of subjects to provide reasonable statistical power. However, even large studies cannot distinguish with any certainty between a very low risk and no risk. Furthermore, without meaningful measurement of prolonged ETS exposure, results might still be inconclusive regarding the question of causation. In the meantime, it is wrong that an ETS/CHD health scare has been blown up out of all proportion in the last few years by a passionate anti-ETS health lobby. Interpretive opinions are not proven facts; they must be challenged and a more balanced point of view presented to the general public.

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Caldwell, A.D.S.

EDITORIAL

Give a dog-end* a bad name

"Exposure to tobacco smoke and 'wellbeing and health' are incompatible. Discuss." At first glance, this hypothetical examination question poses no great intellectual challenge. Cause and effect have been established beyond reasonable doubt, by means of well-designed pro- and retrospective epidemiological studies, between active cigarette smoking and a statistically significant increase in risk of bronchial carcinoma and coronary heart disease (CHD). It has also been asserted that active smoking can increase morbidity and mortality from a host of other pathological conditions affecting almost all physiological systems. A quick glance down the index to our selected abstracts list will testify to that statement. Serious questions have, however, recently been raised in this and other Journals on the reliability of some data seemingly establishing some of these causal relationships. In the previous issue Professor Ashford (J. Smoking-Related Dis. 1992; 3; 263-274) pointed to the very real problems in assessing smoking-related mortality from all causes and suggested that, not infrequently, a degree of interpretative licence appears to have been exercised in arriving at expected conclusions.

If data on active smoking are being occasionally called into question, there are even greater problems concerning passive smoking and environmental tobacco smoke (ETS). Cardiopulmonary disease, asthma, atherogenesis, lung cancer, leukaemia, retarded growth in children – in these and many more instances, a case has been made for ETS as a major aetiological factor. But assessing the impact of ETS is an exercise made hazardous by confounding variables lurking around every statistical corner. In the case of CHD, for example, some 300 risk factors have at some time or other been identified – by what means is it possible to unravel these data and point the finger with any degree of confidence at ETS *per se* as a major causative element?

In this issue, Dr Armitage (pp27-36) tackles the question of ETS and CHD, and his analysis of 12 major epidemiological studies leads him to conclude that the relationship between ETS and increased risk of CHD "is not proven." He has some cogent remarks to make on the suitability of meta-analyses in the assessment/evaluation of the effects of ETS and about publication bias. Papers with a statistically significant result supporting the point of interest are more likely to be submitted and accepted for publication than are those covering larger numbers of subjects, but where there is a null finding. Further difficulties are encountered when determining inter- and intra-population quantitative exposure to ETS. Should domestic exposure alone be measured, or continual but varying exposure over the course of time? How do you compare groups from different sized households both in terms of numbers of smokers and non-smokers and in the actual area of containment? Is exposure accurately determined by salivary or urinary cotinine concentrations? These are questions which urgently need to be addressed in a meticulous manner to stem the flow of poorly researched or analysed data which could ultimately prove to be counter-productive to the overall public health task.

In an article in the Viewpoint series in the Lancet (1992, 340; 1208-1209) Dr Petr Skrabanek points out another fascinating statistical paradox arising from anti-smoking campaigning over the years. The number of deaths in the UK allegedly attributable to smoking has risen from 50,000 per annum in 1962 to 150,000 at present. However, the number of smokers has fallen

*Editor's note: For our American cousins, dog-end = butt.

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from 75% of men and 50% of women in 1958 to 33% and 30%, respectively, 30 years later. What, one is tempted to enquire, is going on? Could it be that smoking is becoming an increasingly convenient scapegoat? In an illuminating couple of sentences, Skrabanek puts it into perspective: "Statements such as 'a half-billion of the world population will be killed by tobacco' are intended to horrify. They tell us nothing about what to advise a 65-year-old widow with rheumatoid arthritis, who smokes 15 a day – *and such information is nowhere to be found.*" (My italics.) Subsequent correspondence (Lancet 1993; 341; 58–59) underscores the importance of resolving such clearly emotional questions.

The Journal of Smoking-Related Disorders is firmly behind all efforts to prevent the young from starting to smoke and convincing older people to stop. But we can also see the dangers inherent in overkill and the use of unsubstantiated generalisations. Campaigners are by nature evangelical in their approach – but the scientific argument has to be built on more solid foundations. To this end, the Editors of the JS-RD together with the publishers, Gardiner-Caldwell Communications (GCC Ltd), are actively canvassing support for an International Congress which will address some of the issues touched upon above. Anyone who would like further information should contact the Managing Editor directly at GCC Ltd, Macciesfield.

Returning to our examination question – it does not, after all, elicit a clear-cut answer. For many, smoking is a pleasurable experience and to many more probably the only pleasurable one left without which their particular 'well being and health' might well suffer deleteriously. That is a fact which certainly the General Practitioner has to take on board when dealing with the individual patient (relevant to the quotation from the Lancet article above). It does and should not in any manner detract from the main thrust of the pathophysiological anti-smoking arguments which will be pursued with vigour in the pages of this Journal.

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WEAKNESSES IN RECENT RISK ASSESSMENTS OF ENVIRONMENTAL TOBACCO SMOKE

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ABSTRACT

Epidemiological evidence of increased lung cancer risk in never smokers married to smokers has been used to estimate annual deaths from environmental tobacco smoke (ETS) exposure. Such estimates are very much higher than those based on dosimetric considerations and misleadingly ignore major weaknesses in the epidemiology. Some authors overestimate total lung cancers occurring in never smokers. There is no scientific basis for extending risk assessments to include deaths from other causes, from workplace exposure to ETS, and among ex-smokers. Recent risk assessments by Wells, by Repace and Lowrey, and by Kawachi and colleagues are given particular attention.

INTRODUCTION

In 1986 four authorities reviewed the evidence on the relationship of environmental tobacco smoke (ETS) and health (1-4). There was agreement that there was inadequate evidence to determine whether ETS caused heart disease or cancers other than the lung. With regard to lung cancer views were more conflicting. The International Agency for Research on Cancer (1), while noting that "several epidemiological studies have reported an increased risk of lung cancer in non-smoking spouses of smokers" pointed to "substantial difficulties" and errors that "could arguably have artefactually depressed or raised estimated risks" so that each study "is compatible either with an increase or with an absence of risk". The Australian National Health and Medical Research Council (2) noted that "the evidence that passive smoking causes lung cancer is strongly suggestive" and, although pointing to difficulties in many studies that "preclude a conclusive interpretation", stated that "passive smoking gives rise to some risk of cancer". The US Surgeon General (3) concluded that "involuntary smoking is a cause of lung cancer" but that quantification of the risk for the US population "is dependent on a number of factors for which only a limited amount of data are currently available". The US National Research Council (4) noted that a "summary estimate from epidemiological studies places the

increased risk of lung cancer in non-smokers married to smokers compared with non-smokers married to non-smokers at about 34%" and considered that, though "to some extent, misclassification bias may have contributed to the results reported in the epidemiological literature", the "bias is not likely to account for all of the increased risk".

Although one of the four authorities felt it premature to conclude cause and effect, and two who thought cause and effect could be concluded, felt it could not be quantified, there has been an increasing tendency to carry out risk assessments to estimate annual numbers of deaths due to ETS. The purpose of this paper is to underline a number of problems in conducting such risk assessments, and to comment critically on three that have recently been published. The first, by Wells (5), estimated that annually in the United States 46,000 deaths per year occurred among non-smokers (i.e. never plus ex-smokers combined) due to ETS exposure at home and at work. 3,000 were from lung cancer, 11,000 from other cancer and 32,000 from heart disease. The second, by Kawachi and colleagues (6), estimated that annually in New Zealand 273 deaths per year occurred among never smokers, 30 from lung cancer and 243 from ischaemic heart disease; 95 deaths were from at home exposure and 178 from at work exposure. The third risk assessment, by Repace and Lowrey (7), was based on a review of nine

other risk assessments for lung cancer. They noted that "excluding one study whose estimate differs from the mean of the others by two orders of magnitude, the remaining risk assessments are in remarkable agreement. The mean estimate is approximately 5000 ± 2400 non-smokers' lung cancer deaths per year in the US".

This paper starts by discussing risk assessment for lung cancer among never smokers based on epidemiological data in relation to spouse smoking, this being the area most intensively studied. Following this problems resulting from extending the risk assessment to cover other diseases are discussed, as are those caused by considering workplace as well as at home ETS exposure. Finally, some other issues are considered.

LUNG CANCER IN NEVER SMOKERS IN RELATION TO ETS EXPOSURE FROM THE SPOUSE

An up-to-date review of the evidence (8) shows there are 27 epidemiological studies of lung cancer (involving nine or more cases) in which risk in never smokers could be related to the smoking status of the spouse (or in five studies to an alternative index of at-home exposure). Eleven studies were conducted in the US, eleven in Asia and five in Europe, involving a total of 2350 lung cancer cases with relevant data, 90% of these being females. 26 of the 27 studies provide estimates of relative risk in relation to this index of ETS exposure for females; values range from just under 1.0 to just over 2.0. Five are statistically significantly positive and 20 estimates are greater than 1.0. Taken as a whole the data show a positive relationship - the median is about 1.25. Based on 17 of these studies, using formal meta-analytic techniques which weighted studies on sample size but not on quality of evidence, Wells (5) gave an average relative risk of 1.44, with 95% confidence limits 1.26 to 1.66. The data for males are more variable, being based on 11 studies often with small numbers of deaths. Seven relative risks were greater than 1, onesignificantly so, with one equal to 1 and three less than 1. The median is similar to that for females.

The epidemiological evidence has been used for the risk assessments of Wells (5) and Kawanishi *et al* (6). It has also been used for a number of the risk assessments cited by Repace and Lowrey (7). This is only valid if the epidemiological evidence itself is sound and not subject to material bias. In order to investigate

this issue, two questions will be addressed; first, "Is the magnitude of the risk plausible based on what is known about the extent of exposure?" and second, "Are there weaknesses and sources of bias in the epidemiology which could invalidate the approach?"

Dosimetric considerations.

If lung cancer risk, relative to a non ETS exposed never smoker, is RE in an ETS exposed never smoker and RS in an ever smoker, then the ratio of excess risks $X = (RE-1)/(RS-1)$ is an indicator of the relative effects of ETS exposure alone and of smoking. Since risk associated with smoking is approximately proportional to number of cigarettes smoked, one might expect, were the epidemiology unbiased, that X would be similar to the ratio of relevant smoke constituents from ETS exposure and from smoking. Table 1 shows, in rank order, estimates of X based on data for 18 studies in females and 7 studies in males. In females, almost half (8/18) of estimates are 0.2 or greater with the median value 0.14. For males, the results vary more and are based on many less data points, but the conclusions to be drawn are similar - namely that the epidemiological evidence, if unbiased, suggests that the extent of exposure from ETS (from spousal smoking) is something like 10-20% of that from active smoking.

It is clear the ratio of exposure from ETS and exposure from active smoking is much lower than 10-20% for those smoke constituents that are commonly used as markers. In a large nationally representative study in the UK (27), mean salivary cotinine levels in non-smokers married to non-smokers, in non-smokers married to smokers and in smokers were respectively 1.22, 3.78 and 331 ng/ml in males and 0.76, 2.21 and 328 ng/ml in females, giving a relative exposure for ETS to active smoking of 0.8% in males and 0.4% in females. Repace and Lowrey (7) give a slightly higher figure, noting that non-smokers have of "the order of 1% of nicotine uptake of smokers" but it is still an order of magnitude less than the 10-20% one requires to align with the epidemiology. Differences in clearance rates of cotinine reported between non-smokers and smokers are too small to affect this gross discrepancy materially; in any case, since the half-life seems to be longer in non-smokers it would increase the discrepancy (28), not reduce it as Repace and Lowrey (7) claim.

TABLE 1 Comparability of relative risks due to ETS exposure (from spouse) and active smoking

Study	(ref)	Sex	RE*	RS**	X+
Inoue	(9)	Female	2.55	4.25	0.48
Geng	(10)		2.16	4.18	0.36
Trichopoulos	(11)		2.08	4.37	0.32
Akiba	(12)		1.52	3.24	0.23
Brownson	(13)		1.82	4.75	0.22
Koo	(14)		1.55	3.56	0.21
Lam 1	(15)		2.01	5.94	0.20
Hole	(16)		1.89	5.43	0.20
Lam 2	(17)		1.65	4.97	0.16
Hirayama	(18)		1.38	4.12	0.12
Gao	(19)		1.19	3.15	0.09
Wu	(20)		1.20	3.31	0.09
Correa	(21)		2.07	14.10	0.08
Humble	(22)		2.34	28.53	0.05
Svensson	(23)		1.26	7.17	0.04
Lee	(24)		1.03	4.70	0.01
Buffler	(25)		0.80	5.91	-0.04
Chan	(26)		0.75	3.07	-0.12
Akiba	(12)	Male	2.10	3.21	0.50
Hirayama	(18)		2.34	4.39	0.40
Hole	(16)		3.52	15.88	0.17
Humble	(22)		4.19	29.36	0.11
Correa	(21)		1.97	30.15	0.03
Lee	(24)		1.31	12.02	0.03
Buffler	(25)		0.51	7.03	-0.08

* Risk of ETS exposed never smoker relative to non ETS exposed never smoker

** Risk of ever smoker relative to non ETS exposed never smoker

+ Ratio of excess risks, e.g. for first study $0.48 = (2.55-1)/(4.25-1)$

N.B. Risks given are unstandardised for age since standardised estimates were not available in many studies and generally differed little from unstandardised estimates where both were available.

Estimates of relative exposure based on inhaled smoking-related particulates show an even greater discrepancy. Arundel *et al* (29) have estimated that for the US average daily inhaled particulate ETS exposure for all never smokers is 0.62 mg/day for men and 0.28 mg/day for women as against 387 mg for men and 311 mg for women who currently smoke. Since ETS exposure of exposed non-smokers is about 3 times that of all non-smokers (27), one can calculate that the ratio of average exposure for ETS to active smoking is about 0.4% in men and 0.2% in women, similar to an estimate of 0.3% given by Repace and Lowrey (7) based on their own work.

Arundel *et al* (29) pointed out retention of smoking related particulates is much higher in smokers (80%) than in non-smokers (11%). They estimated a relative exposure for ETS to active smoking of around 0.03-0.04% (29). Using radiotracer techniques, a similar, very low ratio of 0.02% has been estimated based on particulate

deposition in the trachea-bronchial region (30).

While both ETS and mainstream smoke contain a wide variety of chemicals, and relative exposure of passive and active smokers will vary quite widely according to which chemical is used as the marker - the factor being higher for vapour phase than for particulate phase compounds (31) - there is certainly strong evidence of a marked discrepancy between the epidemiology and dosimetry. Indeed, since it is commonly believed lung cancer in smokers is associated with deposition of particulate matter in the lung - the basis of "tar" reduction programmes - the discrepancy seems very large, by two or even three orders of magnitude.

One implication is that risk assessments based on dosimetric evidence are likely to give substantially lower estimates than those based on the epidemiological evidence. Another implication is that it gives reason to doubt the epidemiology, and to look for sources of bias.

Risk assessments based on dosimetry versus those based on epidemiology.

Let us consider the situation with regard to the three risk assessment papers which are being studied in detail. All three have different approaches.

Kawachi *et al* takes the epidemiology at face value and do not attempt risk assessment based on dosimetric evidence (except *vide infra* to adjust relative risks for at home exposure to those for at work exposure). The discrepancy between the dosimetry and the epidemiology is not even mentioned.

Wells (5) also bases his risk assessment on the epidemiology. However he does note that the mortality observed for passive smoking is "rather high" relative to the deposited dose of particulate, contrasting relative factors for passive to active smokers of 0.25% for "smoke retention" (Arundel's figures cited above suggest 0.03-0.04%) and 2.9% for lung cancer (Table 1 suggests 10-20%). He believes the differences are due to differences in chemistry and physics between active and passive smoking, and essentially does not doubt the validity of the epidemiology.

Repace and Lowrey (7) review risk assessments based both on dosimetric and epidemiological evidence. While this should have revealed major differences between estimates based on the two methods of risk assessment they in fact claim "remarkable agreement". There are many reasons for this erroneous conclusion:

- i) They rejected the estimate of Arundel *et al* (29), based on retained particulate matter, because it differs from the mean of the others by two orders of magnitude.
- ii) They misquote Robins' work in the NRC report (4). They cite his estimates of 2500-5200 US deaths in lifelong non-smokers per year from passive smoking as being dosimetrically based when in fact they clearly are epidemiologically based. Robins also provides much lower estimates of 45-396 deaths based on respirable suspended particulates, but Repace and Lowrey totally ignore these.
- iii) They quote an early paper by Fong (32), which assumed that the extent of exposure from ETS was of order 2% to 8% that from active smoking, a relative factor far higher than indicated by the more recent data summarized in the previous section.
- iv) They omit their own dosimetrically based

estimate because it is "inconsistent with the epidemiology of passive smoking". It is hardly surprising they get "remarkable agreement" if they reject estimates that do not agree!

Table 2 presents the various estimates for the studies reviewed by Repace and Lowrey (7). The epidemiologically based estimates are reasonably consistent and high. The dosimetrically based estimates are much lower. How much lower depends on the smoke constituent used for extrapolation.

Weaknesses of the epidemiology.

Epidemiology is imprecise. Various sources of bias can produce spurious relative risks of 2 or even more (38). Since the relative risks seen for ETS exposure are well within this range, and since they seem inconsistent with the dosimetric evidence, it is important to examine the epidemiological evidence critically. Six potential sources of bias are considered below:

Misclassification of diagnosis.

Of the 27 epidemiological studies of ETS and lung cancer, three were prospective and based diagnosis on death certificates, and only 15 used only (or virtually only) histologically confirmed cases. Faccini (39) has discussed the dangers of misdiagnosis, particularly of primary breast cancer as lung adenocarcinoma. The magnitude and extent of bias from this source is, however, unclear. Random misdiagnosis would tend to reduce the relative risk, but differential misdiagnosis might increase it. In theory differential misdiagnosis might occur if a risk factor for the misdiagnosed disease is correlated with ETS exposure, or if knowledge of ETS exposure by the doctor affects diagnostic procedures, but there is no direct evidence of this.

Misclassification of ETS exposure.

None of the studies had any objective measure of ETS exposure, either from ambient air measurements in the home or workplace or from measurements of levels of smoke constituents in body fluids. All information came from questionnaires. While random misclassification of exposure will tend to dilute associations, it is possible that in case-control studies some recall bias might have occurred, with cases overestimating exposure relatively to

controls in an attempt to rationalize their disease. This would probably have been less important for relatively "hard" questions such as those relating to whether the spouse smoked than for more "soft" questions on extent of exposure.

Publication bias.

There is strong reason to believe (40) that scientists are less likely to submit, and journals less likely to accept, papers showing no association than those showing a positive association. If so, published evidence tends to overestimate the true association of a factor with

a disease. Since ETS has been the subject of much attention in recent years and since a relatively large number of unpublished null studies would be needed to counterbalance the high proportion of studies of spouse smoking and lung cancer showing a positive association, it would seem unlikely non-reporting bias could fully explain the overall positive relative risk. However the fact that the studies showing the highest relative risk are based on significantly smaller numbers of cases than the studies showing the lowest relative risks (8) is consistent with the notion that small null studies do not get published, and suggests some publication bias exists.

TABLE 2 Estimated number of lung cancer deaths occurring in US never smokers from ETS exposure in 1988 (adapted from Repace and Lowrey (7))

Study	(ref)	Method of estimation	Estimate *
Wald	(33)	Epidemiological	5210
Repace & Lowrey	(34)	Phenomenological **	4310
Robins	(4)	Epidemiological	4150
Wigle	(35)	Epidemiological	3650
Kuller	(36)	Epidemiological	3500
Wells	(5)	Epidemiological	2130
Fong	(32)	Dosimetric - 2% to 8% of effect	1860
Russell	(37)	Dosimetric - nicotine	710
Repace & Lowrey	(34)	Dosimetric-respirablesuspended particulates	490
Robins	(4)	Dosimetric +	240
Arundel	(29)	Dosimetric - retained particulate matter	40

* As given in (7), rounded, or converted from estimate for nonsmokers. Dosimetric estimate for Robins study added.

** Based on comparison of lung cancer rates in never smoking SDAs (Seventh Day Adventists) and non SDAs (uncorrected for numerous lifestyle factors on which SDAs and non SDAs are known to differ).

+ Assuming a non-exposed non-smoker inhales the equivalent of 0.01 cigarettes per day. Robins gives 0.0001-0.005 cigarettes per day for the equivalent in terms of respirable suspended particulates.

Poor design of some studies.

Of the 27 studies which provided information on ETS and lung cancer, 24 were of case-control design. There were clear weaknesses in design in a number of the case-control studies. One study (10) did not even state what the control group was. Four studies (9, 12, 21, 25) included some patients or decedents with smoking associated diseases in their control group. More seriously there were systematic differences in study procedure between cases and controls in a number of studies. In three studies where the case might have been alive or dead (13, 22, 41) the controls were not matched on vital status. Two studies (11, 15) used cases and controls from

different hospitals. Two studies (17, 23) interviewed cases in hospital and some or all controls elsewhere. In three studies (13, 21, 22) the proportion of next-of-kin respondents was substantially higher for cases than controls. Although difficult to quantify the effect of such procedural differences it is notable that for females the observed relative risk in the eight studies showing differences was higher (median 1.9) than in the 17 studies where like was being compared with like (median 1.2, p on rank test <0.05). It is also worth noting that three studies (12, 25, 42) obtained a high proportion of responses from next-of-kin and that in one of these (42), no association between lung cancer risk and spouse smoking was seen when the

subject herself reported the information, but a 3-fold relative risk was seen when the information as obtained from a daughter or a son.

Confounding.

There were 22 studies in which the index of ETS exposure used was smoking by the husband. One would have thought that the standard procedure would have been to present an age-adjusted comparison of married never smoking women whose husbands were non-smokers with married never smoking women whose husbands were smokers, and to also present a relative risk adjusted further for other potentially confounding factors known to affect risk of lung cancer. It was clear this standard procedure was not kept to. About half of these studies included unmarried women in their non-exposed group so that there was a confounding between marital status and ETS exposure. Three of the 22 studies (11, 15, 43) and also one of the other five (26) did not adjust for age at all while in three others (10, 17, 21), although cases and controls were age-matched initially, the error was made of failing to age adjust after the never smokers were selected out. Almost half the studies failed to take into account any other confounding factors and of the remainder most looked at only quite a limited number of possible such factors. Those few studies which looked at a reasonable number of confounders were generally those where no significant effect of ETS exposure had been seen anyway. Koo (44) compared never smoking women whose husbands did or did not smoke on a wide range of factors and found that those whose husbands did not smoke were "better off in terms of socio-economic status, more conscientious housewives, ate better diets, and had better indices of family cohesiveness".

Misclassification.

It is amply documented that active smoking is positively associated with lung cancer and also that smokers tend preferentially to marry smokers more often than would be expected by chance. As a result, even if ETS had no effect whatsoever on lung cancer risk, a spurious positive association between spouse smoking and lung cancer risk will be seen if a proportion of ever smokers are misclassified as never smokers (27). The relationship between the magnitude of this bias and the misclassification rate can be calculated theoretically given the degree of between spouse smoking concordance, the observed proportion of ever smokers, the observed proportion of never smokers who are

married to smokers, and the observed relative risk in relation to active smoking. Table 3 shows this relationship for four scenarios: US women, US men, Asian women and Asian men. The misclassification bias is much larger where the proportion of smokers is larger, and where the relative risk in relation to active smoking is larger. In order to achieve a bias of 1.4 for example, one would need less than a 1% misclassification for US men, about a 2% misclassification for Asian men, about a 5% misclassification for US women and about a 30% misclassification for Asian women. Elsewhere (44) I have reviewed in detail the published evidence on the levels of misclassification actually determined in over 100 studies. In studies of self-reported non-smokers under no special pressure to deny smoking, biochemical tests suggested that on average around 4% were actually current smokers, with 1 to 2% current regular smokers. In addition to the misclassified current smokers, studies in which subjects were asked questions on multiple occasions have shown a somewhat larger number of ex-smokers misclassified as never smokers. The evidence is certainly consistent with misclassification bias being of major importance in the US (and European) studies. However there is virtually no good evidence on misclassification rates in Asian populations. There has long been speculation that rates may be particularly high among women in Japan, where smoking is not considered socially acceptable. A survey of Tokyo University freshwomen (46), among whom 55% of smokers reported that their family did not know they smoked, tends to confirm this. However until cotinine studies are conducted to find out the true situation the extent of bias caused by misclassification in Asian studies will remain unclear.

Misclassification also leads to overestimation of the total number of lung cancers among never smokers. This is considered below under "other issues".

Conclusion.

The answers to the two questions posed earlier are clear. The epidemiology has indicated a magnitude of risk in relation to spouse smoking that is implausibly large compared with what is known about the extent of ETS exposure involved. There are clear weaknesses and sources of bias in the epidemiology which could invalidate risk assessments based on it. The most important of these are misclassification bias and failure properly to compare like with

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like in case-control studies, but failure to properly take confounding variables into account and publication bias are also relevant.

All three risk assessments criticised in this document take the epidemiology virtually at face value, with no real discussion at all of its weaknesses. Thus Kawachi *et al* (6) mentions only publication bias (and dismisses it), while Wells (5) considers only misclassification bias (and then inadequately corrects for it). Repace

and Lowrey (7) do not discuss any sources of bias at all (though some of the authors whose studies they review do so). No reasonable scientific criteria are used to decide what constitutes a valid study before it can be included in a risk assessment - studies conducted with complete disregard of basic scientific principles are included as if they were as valid as carefully designed studies.

TABLE 3 Bias due to misclassification in four scenarios.

Scenario	% Ever Smoked	% ETS Exposed	RR for Smoking	Misclassification Rate	Bias
US women	49.0	54.3	6.73	1%	1.06
				2%	1.12
				5%	1.35
				10%	2.02
US men	77.1	38.7	11.83	1%	1.52
				2%	2.38
Asian women	24.5	56.9	2.99	10%	1.07
				25%	1.26
				40%	1.73
				50%	2.82
Asian men	80.8	6.6	3.48	1%	1.20
				2%	1.42
				5%	2.36

N.B. No effect of ETS and between spouse concordance ratio of 3.0 assumed. % ever smoked, % ETS exposed and RR (relative risk) for active smoking estimated from those studies providing relevant data. See (8) for further details.

EXTENDING RISK ASSESSMENT TO COVER DISEASES OTHER THAN LUNG CANCER

Heart disease.

In the risk assessment by Wells (5), heart disease deaths formed 70% of the total. In that by Kawachi *et al* (6), they formed 89%. As noted above, in 1986 none of the major authorities considered that ETS had been shown to cause heart disease. Evidently Wells and Kawachi, in assuming that ETS causes heart disease, are jumping to a conclusion that a number of panels of distinguished scientists have not reached. While there are more data now than in 1986, it remains abundantly clear that the evidence still does not support this conclusion.

Wells (5) cites data from six published studies (18, 24, 47-50) and one unpublished study (51). Of these seven studies, five (16, 24, 48, 50, 51) were based on very much smaller number of

deaths/cases than the other two (18, 49) so that they contribute very little to the overall meta-analysis. While some further small studies have been published since (see 8), none are large. For this reason it is worth taking a detailed look at the two larger studies.

The largest of these studies was by Helsing *et al* (49). This involved more heart disease deaths among non-smokers than all the other studies combined. It reported a 24% increase in heart disease risk in women exposed to ETS, based on 988 deaths, and a 31% increase in men, based on 370 deaths. Many features of the study and the results render any conclusion that ETS causes heart disease most insecure:

- i) The comparison was of people who lived with a smoker and of those who did not, with no direct adjustment for the number of people in the household. Clearly the larger the household, the more likely it is to contain a

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smoker, so any risk factors related to household size could contribute to the association.

- ii) The study was not a properly conducted prospective study, in that data were only collected on whether a given subject had or had not died in Washington County over the 12-year period. Differences in smoking habits and disease status between those who left the county and those who did not may have caused substantial bias.
- iii) There was no dose-response relationship in the exposed groups. Indeed, in men the risks (relative to the non-exposed) were somewhat lower with increasing exposure score.
- iv) Adjustment for effects of age, marital status, years of school and quality of housing used a procedure that was unclear and which had a huge effect. Thus in women, the passive smoke exposed group had a crude heart disease death rate 34% lower than the non-exposed group. After adjustment it was 24% higher. Such a large effect of adjustment makes one wonder just how contingent the reported results were on the exact list of confounding variables included, the statistical technique used for adjustment, and the accuracy with which the confounding variables were measured.
- v) A whole range of factors have been related to heart disease. Among major factors not considered in the study were hypertension and cholesterol level.

While it is difficult to determine the relative importance of the features listed above, it is clear that one must have very considerable reservations about the results from this study.

The Japanese prospective study of Hirayama (18) is superficially very good, being very large, having a long follow-up period and being apparently reasonably representative. However, following detailed scrutiny given to his study following the 1981 paper (52) which really brought ETS to public attention, a number of authors have identified various weaknesses (53, 54, 55). His questionnaire was extremely short and crude by modern standards, severely limiting the number of risk factors studied and the depth to which they could be investigated. The population was only interviewed once with no changes in habits recorded in 16 years. The mortality of his allegedly representative population is too low to reconcile satisfactorily with national rates, indicating that tracing of deaths was incomplete, with deficits varying by age and marital status

(53). His statistical presentation is inadequate in a number of ways: the methods used were not appropriate for analysis of long-term cohort studies; rates for heart disease in women were age adjusted to their husband's age rather than their own age; and some basic mistakes in analysis were made. One error, noted in 1981 (54), resulted in enormous inflation of the significance of the lung cancer association. A second, noted more recently (55), concerned the total inconsistency of results for heart disease reported in 1981 and 1984, and was only resolved by Hirayama (56) admitting his earlier data were in error. A number of approaches have been made to Hirayama to release his data for independent verification of his findings by more appropriate statistical methods, but Hirayama has always refused to release his data, which only casts more doubt on his findings. While his findings show a 16% increased risk of heart disease in never smoking women married to smokers which is marginally significant when a dose-related trend test is used, it is difficult to place much faith in his findings.

Although it has been demonstrated above that the risk assessment for heart disease essentially rests on the results from two studies, both of which seem unreliable, a number of other general points can be made. First, there are a very large number of risk factors for heart disease. It is evident that adjustment for these factors in the studies has always been incomplete, and often seriously incomplete. Second, the extent of the association seen in some of these studies, which in some cases is close to that reported in relation to active smoking, is implausibly high when viewed against the extent of the association seen in relation to active smoking. Third, there is a major danger of publication bias. It is notable that the literature is still relatively sparse despite the numerous ongoing studies of heart disease and the fact that heart disease in a non-smoker is probably 50 times or so more common than lung cancer in a non-smoker. Any prospective study that has reported on lung cancer clearly could have done so for heart disease. The fact that the American Cancer Society million person study, which reported for lung cancer (57), has not reported any results on the relationship of heart disease to ETS can reasonably be read as implying no relationship was found in that study. If this is in fact true, and its results were published, the picture from the meta-analysis would change dramatically since the study would involve so many deaths from heart disease in non-smokers.

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Cancer other than the lung.

Kawachi *et al* (6) did not include deaths from cancers other than the lung in their risk assessments, but Wells (5) did, although he only made estimates for females since he considered data for males to be too sparse. In fact, there is by now rather more evidence available than Wells considered, and the picture is completely unconvincing as to the effect of ETS exposure.

Of 10 studies providing some evidence, six give no real indication of an effect of ETS. These included two moderate sized case-control studies of bladder cancer (58, 59) which both gave relative risks close to unity, a case-control study of cervix cancer (60) which found no association with spouse smoking after controlling for smoking by the female subject, and a prospective study (47) which found a non-significant relative risk of 1.20 for cancers other than the lung based on 43 deaths. Another study showing no effect was the case-control study of Miller (61) from which an age-adjusted relative risk of 0.97 for lung cancer in relation to husband's smoking history could be calculated. It is interesting to note that Miller, while presenting data by age, did not age-standardise, and gave a relative risk of 1.40, while Wells (5), though he did age-standardise, unaccountably used data for unemployed rather than all women, giving a non-significant, relative risk of 1.25. The largest study showing no effect was the Washington County study on which the Helsing heart disease results (49) were based. A later paper (62) reported that relative risks for all cancer for living with a smoker were 1.01 in males, based on 115 deaths, and 1.00 in females, based on 501 deaths.

Turning now to the four studies that provided at least some suggestion of an effect, the smallest was that by Reynolds *et al* (63). This prospective study found no association between smoking by the spouse and risk of cancer in men, not giving detailed results. In women, a positive association was found, but this was only of marginal significance ($p=0.035$), and the relative risk of 1.68 had quite wide confidence limits, being based on only 71 cancer deaths, only five of which were considered to be smoking related.

In a large case-control study of cervix cancer in Utah (64), a significant positive trend in risk was noted in relation to various indices of passive smoking exposure. There were many weaknesses in this study, including failure to adjust for religion (42% of cases and 58% of controls were Mormons); large and differential non-response rates, misclassification of

smoking status, and failure to adjust adequately for sexual habits. A crude relative risk of 14.8 in relation to ETS exposure for three or more hours per day dropped to 2.96 after adjustment for the reported number of sexual partners of the woman. As number of sexual partners is only an inaccurately measured surrogate of the true sexually related cause of cervix cancer, presumably a sexually transmitted infection, the adjustment will be incomplete and the excess relative risk in relation to ETS may be wholly spurious representing a residual confounding effect of sexual habits (65).

The other two studies reporting a positive association were both cited by Wells (5) and were the major contributors to his risk assessment for cancers other than the lung. The study by Sandler *et al* (66) for which Wells cites a relative risk of 2.0 based on 231 cases of cancer other than the lung, used a mixture of friends or acquaintances of patients and people randomly selected by systematic telephone sampling as controls, a very questionable procedure. Response rates also varied substantially between cases and controls. The unconvincing nature of the findings was heightened by study of the results for individual cancer sites where large effects were claimed for ETS for a number of cancers (breast, thyroid, leukaemia/lymphoma) that have little or no relationship to smoking.

The largest study is that by Hirayama (18, 52, 67). Wells (5) cites a relative risk of 1.11 (95% confidence limits 1.0-1.2) based on 2505 deaths from cancer other than the lung. This is unconvincing for a number of reasons. First, most of the comments made about this study when considering the heart disease results apply. Second, the relative risk is only at best of marginal significance (trend $p = 0.05$ on a one-tailed test). Third, the association with spouse smoking arises mainly because of elevated risks of brain and breast cancer, cancers that are not smoking related.

The overall evidence for cancer other than the lung is clearly remarkably unconvincing in demonstrating any effect of ETS exposure. Where any association is reported it is generally for cancer sites not affected by active smoking. Wells (5) has great (and unjustified) faith in the epidemiology, claiming "these differences in mortality effects are probably real." Because it is certainly true (though as yet unquantified) that smokers have higher ETS exposure than nonsmokers it is *a priori* very difficult to see how an association with any disease could be observed only in response to ETS exposure, a

view endorsed by IARC (1). Wells argues competing risks might be the explanation, effects of ETS exposure on such cancers as brain, endocrine glands, lymphoma, and breast only occurring in people with a particular susceptibility, and that people with this susceptibility, if they smoke, die first from lung cancer or other smoking-related cancers. This seems a remarkably unattractive and implausible hypothesis, for which there is no supportive evidence. Mortality patterns for lung cancer in terms of age, dose and duration of smoking are well described by models involving no component for variation in susceptibility at all, the response arising from random variation. Of course susceptibility might in fact vary to some extent (68, 69), but hardly so much that any effect in active smokers would be ruled out. The simpler hypothesis that any relationship seen between ETS and cancer of sites other than lung is due to chance or bias seems more plausible.

EXTENDING RISK ASSESSMENT TO COVER ETS EXPOSURE FROM THE WORKPLACE

Wells (5) took account of ETS exposure outside the home in two ways in his risk assessment. First, he estimated the proportion exposed by adding the proportions of never smokers living with ever smokers (taken from the controls of the US based epidemiological studies) to the proportions of all nonsmokers who did not live with a smoker but who were still exposed at home or at work (taken from Friedman (70)). Second, he adjusted relative risk estimates upwards, except in Greece, Japan and Hong Kong, by assuming that nonexposed nonsmokers were actually exposed to 1/3 the extent of the exposed nonsmokers. Essentially he assumed that exposure outside the home had the same effect as exposure from the spouse.

Kawachi *et al* (6) estimated the proportion of people exposed at home and at work from surveys. From the relative risk in relation to home exposure, 1.3, they multiplied the excess relative risk, 0.3, by a factor, 4.0, based on Repace and Lowrey's estimate (34) of the relative extent of exposure to the particulate phase of ambient tobacco smoke at work (1.82 mg/day) to at home (0.45 mg/day); thus estimating relative risk of lung cancer in relation to work exposure, 2.2. They commented that "this estimate is consistent with the relative risk of 3.3 (95% confidence interval 1.0-10.5) for never smokers exposed to

passive smoking at work reported by Kabat and Wynder (71) in one of the few studies that has distinguished exposure at work from exposure at home. However, we have adopted the more conservative estimate of 2.2".

It is surprising that neither Wells (5) nor Kawachi *et al* (6) seem to have actually taken into account the total epidemiological evidence on lung cancer in relation to workplace exposure. Had they done so (see Table 4) they would have found that overall it gives no indication of a positive association at all, with only four out of eleven relative risk estimates greater than 1.0 and only the single estimate (Kabat 1 - males), selectively cited by Kawachi *et al* (6) even close to being significantly positive. The upper confidence limit for seven of the eleven estimates is less than the estimate of 2.2 used in their risk assessment.

Most lung cancer cases occur at an age after people have retired. While Wells (5) adjusts the exposed fraction down with increasing age, Kawachi *et al* (6) make no such adjustment, assuming that their unjustifiably high relative risk of 2.2 in relation to workplace exposure operates at age 80 as at age 40.

The estimates by Kawachi *et al* (6) of risk due to workplace exposure from risk due to at home exposure are in any case methodologically unsound. Even assuming (and these are very big assumptions), that meta-analysis gives unbiased estimates, that risk is linearly related to extent of exposure to smoke constituents, and that the estimates of relative exposure at work and at home are valid, the equation they used is totally incorrect. The formula only makes sense for a comparison of those exposed at work and not elsewhere with those exposed at home and not elsewhere. If at home and at work exposure are positively correlated (as is likely) double counting of deaths arises. In the extreme situation where everyone is exposed to both or to neither source, their method for estimating deaths due to at home exposure yields an answer appropriate for both exposures combined. Using their procedure, which would then multiply up deaths due to ETS by five, might lead to there being more deaths due to ETS than actually occur in all!

The validity of the factor of 4 for relative exposure at work to at home is anyway very dubious. A recent large survey in London (74) found little difference between particulate matter levels measured in the home and at work. Indeed where smoking took place, the level at work was less than at home.

TABLE 4 Reported relative risks of lung cancer in relation to ETS exposure at work.

Study	(ref)	Sex	Index of exposure	Relative risk (95% conf. limits)
Garfinkel	(42)	Female	Smoke exposure at work in last 5 years	0.88(0.66-1.18)
		Female	Smoke exposure at work in last 25 years	0.93(0.73-1.18)
Kabat 1	(71)	Female	Current exposure on regular basis to tobacco smoke at work	0.68(0.32-1.47)
		Male	Current exposure on regular basis to tobacco smoke at work	3.27(1.01-10.6)
Kabat 2	(72)	Female	Exposed to ETS at work (ever)	1.00(0.49-2.06)
		Male	Exposed to ETS at work (ever)	0.98(0.46-2.10)
Lee	(24)	Female	Passive smoke exposure at work	0.63(0.17-2.33)
		Male	Passive smoke exposure at work	1.61(0.39-6.60)
Shimizu	(73)	Female	Someone at working place smokes	1.20(0.44-1.37)
Varela	(41)	Both	150 person/years smoking in the workplace	0.91(0.80-1.04)
Wu	(20)	Female	Passive smoke exposure at work	1.3 (0.5-3.3)

OTHER ISSUES

Extension of risk assessments to workplace ETS and heart disease deaths.

While the use of epidemiological data to estimate the number of deaths from lung cancer among never smokers is dubious, extension of these estimates to other diseases and to workplace exposure is even more so. This highlights the invalidity of the estimates by Kawachi *et al* (6) where of a total of 273 deaths per year due to ETS among never smokers, only 4 are from lung cancer due to at home ETS exposure, while as many as 152 are from ischaemic heart disease due to at work ETS exposure. The fragility of the confidence limits, 112 to 442, for the overall total of 273 is obvious. In no sense can we be confident that the true answer lies in this range. The estimate is cast in an even poorer light when one realises that the factor of 4 used to calculate lung cancer relative risks at work from those at home is also used for heart disease. What is the justification for that? The basis for the factor is relative particulate matter exposure, widely thought irrelevant to heart disease aetiology. It is notable that their resultant heart disease relative risk estimates for at work exposure are, implausibly, larger than those generally reported in relation to active smoking.

Extension of risk assessments to ex-smokers.

Wells (5) and Repace and Lowrey (7) estimate numbers of deaths due to ETS among never smokers and ex-smokers combined. They

assume risk estimates based on results for never smokers are applicable also to ex-smokers. Neither paper discusses the problems implicit in this approach. In the first place there is no direct epidemiological evidence on risk in relation to ETS exposure for ex-smokers with the limited exception of the study by Varela (41) which found no evidence of an effect of ETS in either never smokers or long term ex-smokers. Nor is there any evidence on levels of ETS exposure in ex-smokers as distinct from never smokers. Without direct evidence the assumption that risk increases in relation to level of ETS exposure in ex-smokers to the same extent that it does in never smokers seems remarkably simplistic. Might not effects of ex-smoking interact with those of ETS (if any)? Might not the situation depend on how long ago the smoker has given up, or why? There seems no scientific justification whatsoever for extrapolating estimates to ex-smokers.

Extrapolation from one country to another.

Kawachi *et al* (6) do not discuss the validity of calculating estimates for New Zealand when all their relevant source data comes from other countries. Their answer depends heavily on the US based factor of 4 used for relative exposure at work to at home. As noted above a UK study (68) found a factor less than 1. Which is relevant for New Zealand?

Variations in relative risk of lung cancer by age.

As discussed by Wells (5) and in the NRC report by Robins (4), if the relationship between

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ETS and lung cancer risk depended on age, it would be appropriate to take this into account in the risk assessment. In fact only the study of Hirayama (18, 67) presents data by age, other investigators implicitly assuming that the relative risk is invariant of age. Using a relative risk estimate of 1.44 as applying to all age groups, Wells calculated there would be 992 deaths per year due to ETS exposure. Wells noted that Hirayama's data actually indicated "a declining relative risk with age from 1.87 at approximately age 50 to 1.43 at approximately age 75" and used these data to "develop a second death calculation assuming a declining relative risk but still normalized to 1.44" arriving at a slightly lower estimate of 911 deaths per year. Wells' calculations mislead in a number of ways. First, he used as source material data on risk by age of the husband (67) when more appropriate data by age of the wife were available (18). Second, he used data for ages 60-69 and 70-79 combined as applicable at "approximately age 75", concealing the fact that the relative risk estimate at age 70-79 is actually 0.70. If one uses data in Wells' Table 6 for never smoker death rates, nonsmoker populations and fractions exposed by age, and one uses Hirayama's actual relative risks by age of the wife (18), then it can be shown (Table 5) that allowing for variation in risk by age very substantially affects estimates. Thus, for the 40-79 age group, one arrives at an estimate of 858 deaths due to ETS if one assumes age invariance,

but one actually arrives at an estimate of 964 deaths saved by ETS if one uses Hirayama's data directly. The relative risk estimate for the 70-79 year age group is certainly unreliable, being based on only 6 deaths in the Hirayama study (as against 46, 91 and 57 for ages 40-49, 50-59, 60-69), so in Table 5 estimates of deaths are also shown using a combined relative risk for the age groups 60-69 and 70-79. This gives an estimate of 299 deaths due to ETS, substantially less than that assuming risk is invariant of age. While there are many problems in applying the Hirayama estimates, including the fact that Wells' Table 6 is based on age at death whereas Hirayama's data are based on age at start of the study, Wells' paper conceals the major problems which have been given detailed attention by a number of authors (75, 76). Reliable data broken down by age are clearly needed.

How many lung cancer deaths are there in total among never smokers?

In 1985 in the USA, there were a total of 83,854 deaths from lung cancer among males and 38,702 among females (77). In his Tables 6 and A1, Wells (5) gives estimates of death rates among never smokers which, if applied to the age-specific population estimates of never smokers, yield 1,907 deaths among males and 4,232 deaths among females, respectively 2.3% and 10.9% of the total deaths from lung cancer.

TABLE 5 Numbers of lung cancer deaths per year among US nonsmokers occurring in the population aged 40-79 based on Hirayama's (18) estimates of relative risk by age of wife

Age	Risk assumed invariant of age		Risk assumed to vary with age	
	Relative risk	Deaths	Relative risk*	Deaths*
40-44	1.45	32	2.76	69
45-49	1.45	40	2.76	85
50-54	1.45	58	1.72	79
55-59	1.45	89	1.72	122
60-64	1.45	119	1.12(0.97)	39(-11)
65-69	1.45	165	1.12(0.97)	54(-15)
70-74	1.45	170	0.19(0.97)	-740(-15)
75-79	1.45	185	0.19(0.97)	-672(-15)
Total		858		-964(299)

* Bracketed items assume common estimates for 60-69 and 70-79 age group.

Elsewhere (78), I have reviewed the proportion of lung cancers occurring among never smokers in a range of recent epidemiological studies of Western populations. This gave an average of 2.4% for males and 13.2% for females, equivalent to 2,012 and 5,109 deaths

respectively, reasonably close to the estimates of Wells.

Other authors have suggested there are more deaths than this. Thus in the 1986 NRC report (4) Robins quoted estimates of roughly 5,200 deaths for males and 7,000 for females among U.S.

never smokers in 1985, while Repace and Lowrey (7) cite Kuller *et al* (36) for an estimate of 6000 to 8000 lung cancer cases each year in US never smoking women.

Three points arise. First, there is considerable uncertainty about the number of lung cancer deaths among never smokers.

Second, if the lower estimates, which total about 6,000-7,000 deaths in the two sexes combined, are used, then many of the epidemiologically based estimates shown in Table 2 are totally unreasonable. Even if (implausibly) everyone were assumed to be exposed to ETS with risk doubled as a result the estimated number of lung cancer deaths occurring among never smokers would only be 3,000-3,500, and yet the four highest estimates in Table 2 all exceed this.

Third, none of the estimates of total lung cancer deaths among never smokers cited above make any adjustment for misclassification of smoking status, all taking self-reported smoking habits at face value. Starting with the first estimate cited above of 6,139 deaths for the sexes combined, one can readily calculate that, if 1% of ever smokers were assumed to deny smoking on interview, this figure would fall by over a thousand to 4,972. This underlines the unreasonableness of the higher estimates in Table 2.

DISCUSSION

In the USA in 1985 there were some 120,000 deaths from lung cancer. Although estimates of the total number occurring among never smokers of up to around 12,000 have been cited, more reasonable estimates seems to be about 5,000 to 6,000. In attempting to estimate how many of these occur as a result of ETS exposure, one has to decide whether to base one's estimate on the epidemiological evidence on ETS and lung cancer or on the dosimetric evidence on exposure to relevant smoke constituents of ETS exposed nonsmokers and smokers. It is abundantly clear that the two methods of estimation give very

different answers. Thus, while estimates based on retained particulate matter give tens of deaths and those based on nicotine or respirable suspended particulates give hundreds, the epidemiologically based estimates all give thousands of deaths. Which answer, if any, one accepts depends to a large extent on the faith one places on the different types of evidence. Wells (5), Kawachi *et al* (6) and Repace and Lowrey (7) accept the epidemiology essentially at face value and pay little or no attention to its poor quality and very obvious weaknesses. They either ignore the dosimetric evidence (6), do not make it clear that it gives different answers and/or dismiss it as inconsistent with the epidemiology (7), or invoke mechanisms to explain the discrepancy which are scientifically unappealing (5). It seems to this author that the epidemiological evidence is untrustworthy and that, between the two, the dosimetric evidence is preferable. Of course problems remain both in choosing the appropriate index of exposure to use and in selecting the appropriate dose response curve at low doses (with the possibility of a threshold), but it seems clear that this approach is better than one which leads to such implausibly high figures.

When one restricts attention to lung cancer, to never smokers and to ETS exposure from the spouse, one is at least operating in an area where the epidemiological evidence indicates an association. When one extends risk assessment to other diseases, to ex-smokers and to ETS exposure in the workplace one is stretching the limits of what is science. There essentially is no evidence on possible effects of ETS in ex-smokers and little reason to expect that any effects, if they exist, will be the same as in never smokers. There is some evidence on ETS exposure in the workplace, but this shows no association at all with lung cancer risk. The epidemiological evidence on ETS in relation to deaths from causes other than lung cancer is unconvincing, and no scientific authority has claimed cause and effect.

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P.N. Lee

Environmental **Tobacco Smoke** **and Mortality**

A Detailed Review of Epidemiological Evidence Relating Environmental Tobacco Smoke to the Risk of Cancer, Heart Disease and Other Causes of Death in Adults Who Have Never Smoked

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5.1 Studies Providing Data

Eleven studies have provided information on the relationship of ETS to risk of cardiovascular disease. Seven of these are prospective studies, 5 conducted in the USA (Butler, Garland, Humble II, Sandler II, Svendsen), 1 in Japan (Hirayama) and 1 in Scotland (Hole). Four are case-control studies, 2 in the USA (Martin, Palmer), 1 in China (He) and 1 in England (Lee).

Three prospective studies which have reported results for lung cancer (Garfinkel I), total cancer (Reynolds) or all-cause mortality (Vandenbroucke) have not reported results for heart disease. While the numbers of deaths would not be substantial for the last 2 studies, the fact that the first, the American Cancer Society million person study, has not provided information is a wastage of resource. This study alone would certainly have had data on more deaths/cases than all the 11 published studies combined.

5.2 Features of the Studies Included

It should be noted that very little information is available for 3 of the 11 studies considered: the prospective study of Butler, and the case-control studies of Martin and Palmer for which the only published data consist of abstracts.

The number of deaths/cases in some studies is very small. There are 4 studies with extremely small numbers (Svendsen, 13; Garland, 19; Martin, 23; He, 34), 4 with quite small numbers (Humble II, 76; Butler, 80; Hole, 84; Lee, 118), and 1 (Palmer, 336 in ever smokers and never smokers combined) which, though of moderate size, has not presented findings in a form to allow proper evaluation. Considering the prevalence of heart dis-

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case among never smokers – very much higher than from lung cancer – it is surprising that by now there are only 2 published studies for reporting results based on reasonably substantial numbers of deaths/cases (Hirayama, 494; Sandler II, 1,358).

Of the 7 prospective studies, 4 involved study subjects attending for an examination during which blood pressure, cholesterol and body mass index were measured. It is unfortunate that neither of the 2 substantial studies collected information on these classical risk factors for heart disease. The factors used by the authors for adjustment – occupation by Hirayama, and schooling, housing quality and marital status by Sandler II – are not those which first occur as being most relevant in a study of heart disease.

Some of the studies have problems regarding representativeness of the subjects. Thus, in both the Garland and Hole studies, about 20% of the population did not attend for examination, with a possibility of bias if failure to attend was associated both with ETS exposure and risk of death from heart disease. In the large Sandler II study, only deaths in Washington County were recorded, again imparting a danger of bias if ETS is associated with the chance of migration out of the county. The Svendsen study was based on the well-known Multiple Risk Factor Intervention Trial, which involved people at very high risk of heart disease based on their smoking, blood pressure and cholesterol levels. Since the paper concerned never smokers, all the subjects involved most probably exhibited abnormally high blood pressure and/or cholesterol levels. The Butler study involved Seventh-Day Adventists, an atypical population with regard to many variables.

The 2 studies which provided data on by far the largest number of deaths are both open to criticism, as detailed in sections 2.2.2 (Hirayama) and 2.2.7 (Sandler II), and also in section 4.2.1. It is interesting to note that both studies have published inconsistent results for women. In 1981, Hirayama presented results showing no association of heart disease with husband smoking, based on follow-up of his population to 1979. In 1984, he reported results which showed a significant association, based on follow-up of his population to 1981. These results implied an implausibly strong relationship of heart disease to smoking by the husband when deaths occurring in 1979–81 were considered (a fact pointed out by Lee in correspondence in the *New Zealand Medical Journal* [26, 27]). As a result, Hirayama published revised figures for follow-up to 1979, indicating that the data published in 1981 were incorrect.

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Helsing et al. [40] and Sandler et al. [43] have both presented (in Table 4 of each paper) results for risk of arteriosclerotic heart disease in relation to ETS exposure. Based on identical numbers of deaths and stated adjustment factors, the reported relative risks and confidence limits for men were identical. Inexplicably, however, this was not the case for women, where relative risks and confidence limits both varied. Given the relatively larger contribution of the Hirayama and Sandler II results to the overall number of heart disease cases studied, such differences in reported findings are rather disconcerting.

5.3

Results

Table 5.1 summarizes results for exposure to ETS from the spouse or in the household. Before considering the findings, some points are worth noting:

- (i) As far as can be ascertained, all the relative risks are for never smokers.
- (ii) The index was based on smoking by the spouse in 7 studies (Butler, Garland, He, Hirayama, Humble II, Lee, Svendsen), only married women being considered, except perhaps in the Chinese study where single women were included with the wives of non-smoking husbands. In 2 studies (Martin, Palmer) the index used is not known. The Hole study compared people living at the same address as a study participant who had ever smoked with people who lived at the same address as a study participant who had never smoked, with no other study participant at that address ever having smoked. The Sandler II study used a complex index of exposure, but for the results in Table 5.1 it amounted to a comparison of people living in the household where some adult had ever smoked with people in a household where no adult had ever smoked.
- (iii) When a study has presented different findings at different time points for apparently the same comparison, the later publication has been used, namely, Hirayama [23] and not his 1981 paper [2], and Sandler et al. [43] and not Helsing et al. [40].
- (iv) If the authors have presented adjusted relative risks these have normally been given in Table 5.1. There are some exceptions. First, the relative risk of 14.9 by Garland et al. [38], adjusted for age, systolic blood pressure, total cholesterol, obesity index and years of marriage,

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Table 5.1 Heart disease risk in never smokers in relation to spouse/household smoking

Study	Sex	Cases		Relative risk (95% limits)	Factors ¹ adjusted for
		U	E		
Butler	F	20	60	1.05 (0.65-1.70)	Age
Garland	F	2	17	3.51 (0.80-15.3)	None ²
He	F	9	25	1.50	See text
Hirayama	F	118	376	1.15 (0.94-1.42)	Age of wife
Hole					
Gillis et al.	F	2	19	3.56 (0.83-15.4)	None ³
	M	18	14	1.30 (0.64-2.64)	None ³
Hole et al.	M+F	30	54	2.01 (1.21-3.35)	Age, sex, class, BP, chol, BMI
Humble II	F	27 ⁴	49	1.59 (0.99-2.57)	Age, sex, BP, chol, BMI
Lee	F	22	55	0.97 (0.56-1.69)	None ³
	M	26	15	1.34 (0.64-2.80)	None ³
Martin	F	— 23 —	—	2.6 (1.2-5.7)	None ²
Palmer	F	— ? —	—	1.2 (significance unknown)	Not known
Sandler II	F	437	551	1.19 (1.04-1.36)	Age, schooling, housing, marital status
	M	248	122	1.31 (1.05-1.64)	
Svensden	M	8	5	2.23 (0.72-6.92)	Age, BP, chol, wt, drinks, education

U = Unexposed; E = exposed.

¹ BP = blood pressure; chol = cholesterol; BMI = body mass index; wt = weight.² See text.³ Adjustment for age had little effect, and adjusted 95% limits could not be calculated.⁴ Numbers of cases are approximate, based on age-adjusted rates.

has not been used. It would be incredibly unstable (estimated 95% limits, about 0.2-500), since it is probably impossible to adjust properly for multiple factors with so few deaths. Mantel [pers. commun.] has also said that 14.9 was an error, the appropriate value being log_e (14.9) or 2.71!

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Secondly, unadjusted relative risks have been used for the individual sex results from the Hole study (published in Gillis et al [29]), since age standardization had very little effect and relative risks could only be properly calculated for the unadjusted data.

- (v) The relative risk given in the He study [102], a case-control study in which there was matching on age, race, place of residence and occupation, is adjusted for previous and family history of hypertension, family history of coronary heart disease, amount of exercise, history of drinking, and hypercholesterolaemia. Confidence limits could not be calculated, but the relative risk was stated to be significant ($p < 0.01$), but this seems not to be true (see section 2.7.1).
- (vi) The results presented in Table 5.1 for the Hirayama study are for ischaemic heart disease. Hirayama [20] notes that no significant relationship was seen between spouse smoking and risk of 'other heart disease' (undefined), based on 680 deaths, or risk of hypertensive heart disease, based on 226 deaths. Relative risk estimates were not provided for these two disease categories.

Table 5.1 provides 4 independent relative risk estimates for men and 10 for women, 13 of which are greater than 1, with 4 of them significant: both the male and female estimates for the Sandler II study; and the female estimates for the He and Martin studies. Hole also showed a significantly increased relative risk when results for the sexes were combined. Although an overall estimate of relative risk (as for example calculated by Wells [7]) is probably of little meaning given the extreme variability in study designs and populations involved, the data in this table – considered without regard to study design and a variety of other methodological problems – indicate a weak association between exposure to ETS from the spouse or in the household and risk of heart disease.

Five of the 11 studies provided some information on risk of coronary heart disease and extent of exposure to ETS from the spouse or in the household (Table 5.2). The Hirayama and He studies both showed evidence of a dose-response relationship, with a significant ($p < 0.05$) trend and elevation in risk for women whose husbands smoked 20 or more cigarettes a day. The Hole and Svendsen studies also showed the highest risk in the highest exposure group, though here numbers of deaths were small and the trend statistic was not significant. In the large Sandler II study there was no evidence of a relationship of risk to ETS exposure in either sex, risk of heart disease being similar in those classified as exposed to light or heavy ETS exposure.

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Table 5.2 Heart disease risk in never smokers in relation to extent of spouse/household smoking

Study	Sex	Exposure	Cases	Relative risk	Factors adjusted for
Hirayama	F	Husband: never smoker	118	1.00	Age of wife
		ex-smoker or current			
		1-19 cigs/day	240	1.08	
		current 20+ cigs/day	136	1.30	
He	F	Husband: never smoked during marriage	9	1.00	Cases and controls matched for age, race, occupation, residence
		smoked 1-20 cigs/day	12	2.30	
		smoked 21+ cigs/day	13	6.86	
Hole	F	Household smoking: none	3	1.00	Age
		low	14	2.09	
		high (cohabitant 15+ cigs/day)	16	4.12	
Sandler II	F	Household exposure (score): 0 (none)	437	1.00	Age, schooling, housing quality, marital status
		1-5 (light)	252	1.20	
		6+ (heavy)	299	1.27	
	M	0 (none)	248	1.00	
		1-5 (light)	56	1.39	
		6+ (heavy)	66	1.24	
Svendsen	M	Wife: did not smoke	8	1.00	None
		smoked 1-19 cigs/day	1	0.90	
		smoked 20+ cigs/day	4	3.21	

Information on heart disease in relation to other indices of ETS exposure is fairly sparse. In the Lee study, subjects were classified on a score ranging from 0 to 12 according to whether they considered they were exposed not at all (0), a little (1), average (2), or a lot (3-12), separately for at home, at work, during travel, and during leisure. No significant relationships were seen, relative risk estimates for scores 0-1, 2-4 and 5-12 being 1, 0.43 and 0.43 in males (based on 30 deaths), and 1, 0.59 and 0.81 in females (based on 36 deaths).

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Table 5.3 Effect of adjustment for various factors on estimated relative risk of heart disease in never smokers according to spouse/household smoking

Study	Sex	Adjustment factors	Relative risk (95% limits)
Butler	F	None	1.36 (0.82-2.25)
		Age	1.05 (0.65-1.70)
He	F	Matching factors (age, race, residence, occupation) only	3.52 (1.43-8.65)
		Matching factors, also previous and family history of hypertension, family history of CHD, exercise, drinking, hypercholesterolaemia	1.50
Hirayama	F	None	1.00 (0.81-1.23)
		Age of wife	1.15 (0.94-1.42)
		Age of husband	1.15 (0.93-1.41)
		Age and occupation of husband	1.16 (0.94-1.43)
Hole	F	None	3.56 (0.83-15.4)
Gillis et al.		Age	3.25
	M	None	1.30 (0.64-2.64)
		Age	1.29
Hole et al.	M + F	Age	1.75 (1.10-2.83)
		Age, sex, social class, BP, chol, BMI	2.01 (1.21-3.35)
Humble II	F	Age	1.34 (0.84-2.21)
		Age, BP, chol, BMI	1.59 (0.99-2.57)
Lee	F	None	0.97 (0.56-1.69)
		Age, marital status	0.93
	M	None	1.34 (0.64-2.80)
		Age, marital status	1.24
Sandler II	F	None	0.66 (0.59-0.75)
		Age, housing quality, schooling, marital status	1.19 (1.04-1.36)
	M	None	1.17 (0.95-1.46)
		Age, housing quality, schooling, marital status	1.31 (1.05-1.64)
Svendsen	M	None	2.12 (0.69-6.46)
		Age, BP, chol, wt, drinks/week, education	2.23 (0.72-6.92)

BMI = Body mass index; BP = blood pressure; chol = cholesterol; CHD = coronary heart disease; wt = weight.

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In the Svendsen study, a relative risk estimate, adjusted for age and wife's smoking status, of 2.6 ($p = 0.23$; 95% limits, 0.5-12.7) was derived when men whose co-workers smoked were compared with men whose co-workers did not. This result, and that in Table 5.1, was for coronary death. Svendsen also provided results for the end-point fatal or non-fatal coronary event. Here, relative risk estimates were derived for four categories: (a) neither wife nor co-worker smoked, 1.0 (base); (b) co-worker smoked but not wife, 1.0; (c) wife smoked but not co-worker, 1.2; (d) both wife and co-worker smoked, 1.7.

No result was significant. In the study by Butler which, in the AHSMOG cohort, related heart disease risk to the number of years lived and the number of years worked with a smoker, some 'suggestion' or 'indication' of an effect was reported in both sexes, but no detailed results were reported.

No other study provided information on other indices of exposure. In the study by He, relative risks of 1, 1.88, 3.07 and 5.49 were reported in relation to 0, 1-10, 11-20 and 21+ years of ETS exposure, and relative risks, of 1, 1.54, 2.30, 5.07 and 12.67 were reported in relation to 0, 1-199, 200-399, 400-599 and 600+ cigarette-years of smoking by the husband. Both trends were statistically significant ($p < 0.01$).

Leaving aside the Garland study for reasons noted in subsection (iv) above, 7 studies provided some information on the extent to which adjustment for various risk factors affected the estimates of heart disease risk in relation to spouse/household smoking. The results are summarized in Table 5.3.

Two main conclusions can be drawn from this table. First, that in some studies age adjustment made a substantial difference to the relative risk. This effect, which would depend on the design of the study and on the frequency of smoking by age and sex in the country concerned, is evident in the Hirayama study and is also probably a contributor to the large association reported in the Sandler II study.

The second main conclusion is that there is no clear effect from additional adjustment for the classical coronary risk factors. Thus, while the Hole, Humble II - and perhaps the Svendsen - studies showed some increase in relative risk after adjustment, the He study showed a substantial decrease.

Some of the prospective studies cast more light on the possibility of confounding by various risk factors, since they present data comparing exposed and non-exposed women at the start of the study. The results are

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Table 5.4 Comparison of heart disease risk factors in ETS-exposed and non-ETS-exposed subjects

Study	Sex	Risk factor		Spouse/household exposure		Significance
				no	yes	
Sandler II	F	School grade (12+)	(%)	33.8	35.4	p < 0.1
		Housing index (8-10)	(%)	83.3	81.1	p < 0.01
	M	School grade (12+)	(%)	38.0	43.8	p < 0.01
		Housing index (8-10)	(%)	83.8	80.4	p < 0.05
Garland	F	Years of marriage	Mean	36.0	34.2	p < 0.1
		Systolic blood pressure	Mean	140.1	138.2	NS
		Obesity index	Mean	3.50	3.43	NS
		Plasma cholesterol	Mean	225.7	226.7	NS
Svendsen	M	Diastolic blood pressure	Mean	103.1	103.3	NS
		Systolic blood pressure	Mean	150.8	152.3	NS
		Serum cholesterol	Mean	264.4	266.0	NS
		HDL cholesterol	Mean	42.7	43.4	NS
		LDL cholesterol	Mean	167.1	166.5	NS
		Weight (lbs)	Mean	190.4	194.6	p < 0.05
		Drinks/week	Mean	7.6	9.7	p < 0.01
		Education (years)	Mean	14.2	13.8	p = 0.05
		Income (\$ 000)	Mean	22.3	22.1	NS

HDL = High density lipoprotein; LDL = low density lipoprotein.

summarized in Table 5.4. Significant differences were seen in respect of weight (ETS-exposed heavier), drinks per week (ETS-exposed drink more), housing index (ETS-exposed worse), and years of education (ETS-exposed more in Sandler II, less in Svendsen), but it is not clear that these differences were large enough to cause substantial bias. The Chinese case-control study of He also reported differences in blood fat and apolipoprotein levels according to ETS exposure, but did not attempt to adjust for these in the analysis.

One risk factor which might be relevant, but which was not investigated, was the number of cohabitants. In the Sandler II and Hole studies the index of ETS exposure seemed by its very construction to be correlated with the number of cohabitants. In particular, the Sandler II study would

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Table 5.5 Effect of other variables on estimated relative risk of heart disease in never smokers according to spouse smoking

Study	Sex	Variable/level	Relative risk ¹ (95% limits)	Factors adjusted for
Hirayama	F	Age of wife:		None
		40-49	0.87 (0.47-1.62)	
		50-59	1.03 (0.72-1.46)	
		60+	1.30 (0.98-1.73)	None
		Age of husband:		
		40-49	1.34 (0.74-2.42)	
		50-59	1.25 (0.81-1.92)	Age of husband
		60+	1.07 (0.83-1.40)	
		Occupation:		
Humble II	F	agricultural worker	1.32 (0.99-1.74)	Age, BP, chol., BMI
		other	0.99 (0.72-1.35)	
		Blacks	1.78 (0.86-3.71)	
		High social status Whites	1.97 (0.72-5.34)	BMI
		Low social status Whites	0.79 (0.32-1.96)	

BMI = Body mass index; BP = blood pressure; chol = cholesterol.

¹ For wives whose husband smoked compared to those whose husband did not smoke.

have included all people living on their own in the non-exposed group, and both studies were very likely to include people living in homes with many occupants in the exposed group. Since household size may correlate with many facets of disease, it seems to be a statistical error not to adjust for it in analysis.

Two studies provided some information on variation in relative risk according to the level of some risk factors. Results are summarized in Table 5.5, and show how the association with ETS exposure varies by age and occupation in the Hirayama study and by race and social status in the Humble II study. Although the association with spouse smoking is evident only in agricultural workers in the Hirayama study and only in Blacks and high social status Whites in the Humble II study, there is in fact no significant heterogeneity between the relative risk estimates in either study.

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5.4

Discussion and Conclusions

Although lung cancer is a rare cause of death in those who have never smoked, heart disease is not, and it is much easier to conduct an adequately large study for heart disease than for lung cancer. Yet there are far more studies of ETS and lung cancer than of ETS and heart disease. It is striking that so many of the latter studies are based on very small numbers of deaths or cases and/or have not been properly reported in the literature.

Only 2 studies are sufficiently large to pick up a moderate increase in risk as statistically significant, and neither is satisfactory. Both lack data on classical heart disease risk factors, such as blood pressure, cholesterol and body mass index, and both have a number of problems that have been referred to in detail earlier. Certainly, neither is a straightforward prospective study conducted according to acceptable methodology, with collection of risk factor data at intervals and essentially complete follow-up of deaths.

Apart from the generally unimpressive nature of the studies that have been conducted, the other circumstance that stands out is that 13 of the 14 sex-specific estimates of relative risk of heart disease for spouse or household exposure in Table 5.1 show a positive (though for the most part not statistically significant) association. In considering this fact, a number of points have to be taken into account:

- (i) Active smokers have an increased risk of heart disease, as is clear from numerous epidemiological studies. However, the relative risk is much lower than it is for lung cancer. For example, the 1989 US Surgeon General's report [71] cites results from the latest American Cancer Society prospective study showing that, compared with never smokers, current smokers have relative risks of heart disease of 1.94 in males and 1.78 in females, as compared to relative risks of lung cancer of 22.36 in males and 11.94 in females.

Vapour phase components of cigarette smoke have been implicated in the aetiology of heart disease (rather than particulate phase components for lung cancer [1]), and the relative exposure of ETS-exposed non-smokers as compared with active smokers is substantially higher for vapour phase than for particulate phase components, but the low relative risks for heart disease for active smoking strongly suggest that if ETS does increase risk of heart disease this increase would be quite modest. The six estimates of over 1.5 in Table 5.1 seem difficult to

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reconcile with the dosimetry, especially bearing in mind that active smokers have very substantial ETS exposure.

- (ii) Heart disease is certainly multifactorial, and many of the risk factors have not been taken into account in many of the studies. Confounding is therefore a possibility, particularly in the 2 studies (Hole, Sandler II), where the index of ETS exposure used was likely to be extremely strongly correlated with household size. While the evidence discussed in Tables 5.3 and 5.4 does not clearly demonstrate important confounding by blood pressure, cholesterol or body mass index it is rather limited and somewhat inconsistent. More evidence is clearly needed on this important potential source of bias.
- (iii) Bias due to misclassification of active smoking status is likely to occur, but since the increase in risk in relation to active smoking is relatively so much less for heart disease than for lung cancer, the extent of the bias will be that much smaller. Since the bias is proportional to the excess risk (see section 3.4.9), its magnitude will be only 5-10% of that illustrated in typical situations for lung cancer.
- (iv) Publication bias is one major source of bias that can certainly not be excluded as relevant. There are two major reasons for believing this may be an important issue. First, there is a strong tendency in Table 5.1 for the large relative risk estimates to be based on very small studies. From the 13 sex-specific estimates, the rank correlation is highly significantly ($p < 0.05$) negative. Who would bother to try to publish a paper showing no association based on very few deaths?

Secondly, certain studies that could publish findings have not done so. Of particular importance is the fact that the first American Cancer Society study of over a million men and women, which published results for ETS and lung cancer in 1981, has never published results for ETS and heart disease. It is very likely that no association was found. If this were so, it would have a very large effect on the results of any meta-analysis (or consequent estimate of heart disease deaths 'due to ETS').

Mainly because of the problems caused by the strong likelihood of severe publication bias, it cannot be concluded from the existing evidence that ETS is associated with heart disease. The present author understands that the American Cancer Society intends to publish within the next year or so findings related to ETS based on its second large prospective study. It is hoped that results from its first prospective study will also be released. Until there is such evidence, and hopefully also evidence from other studies involving substantial numbers of deaths from heart disease with good

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control of confounding and with evidence on ETS exposure from sources other than the spouse or in the home, it is certainly premature to come to any conclusions.

Note Added in Proof

Since this section was completed, Dobson et al. [166] reported results from an Australian case-control study of myocardial infarction and sudden death. Among non-smokers there was no positive relationship of risk to ETS exposure at work in either sex. Nor was there a positive relationship of ETS exposure at home in males. In contrast, in females a significant positive relationship of risk was reported to ETS exposure at home. In this study, data on smoking habits were collected by completely different methods for cases and controls, the potential of bias being underlined by the wide variation in smoking frequency reported in controls according to how and where the data were collected. In addition, virtually no relevant confounding variables were taken into account.

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Environmental Tobacco Smoke Exposure and Occupational Heart Disease

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In 1991, the Occupational Safety and Health Administration (1) requested information on exposures and potential adverse health effects that may be associated with poor indoor air quality in the work environment, including information on exposure to environmental tobacco smoke (ETS). One review article, which focused on heart disease and which was published prior to the agency's request, concluded as follows: "the combination of epidemiological studies with demonstration of physiological changes with exposure to ETS, together with biochemical evidence that elements of ETS have significant adverse effects on the cardiovascular system, leads to the conclusion that ETS causes heart disease" (2). Others, however, have expressed conflicting interpretations of human and animal studies on ETS, concluding that it has not been scientifically demonstrated that ETS exposure increases the risk of heart disease in nonsmokers (3,4). The ongoing debate should not only consider the claimed association between ETS work exposure and heart disease in particular, but also occupational heart disease in general. The primary purpose of this chapter is to review the toxicological basis for identifying chemical substances that may be associated with heart disease in the workplace.

At the outset, it should be emphasized that proof of an association between ETS workplace exposure and heart disease is a complex process. Workers, such as garage attendants, may be exposed to one or more substances (such as carbon monoxide) found both in ETS and in other sources, so the total exposure is the sum of two or more sources, for example, vehicular emissions, ambient air pollution, and ETS. The same group of workers may have varied personal habits that have been reported to be associated with heart disease, such as consumption of cholesterol and fats and xanthine beverages at the employee's cafeteria, physical inactivity on the job, and job-related stress. Outside the workplace, there are additional potential risk factors for heart disease, such as lack of leisure time exercise, dietary cook-

ing fat and salt content, household exposure to cooking gas, gas heaters, and household solvents. Other major risk factors reported for heart disease include the worker's familial history of heart disease, diabetes, hypertension, hyperlipidemia, and obesity. Any conclusion on a possible role of ETS in heart disease necessitates controlling for such risk factors.

INVESTIGATIVE METHODS FOR INDUSTRIAL CHEMICALS

Although there are over 300 potentially hazardous chemicals in the workplace, there are less than three scores of industrial chemicals that have been suggested to be associated with heart disease such as ischemic heart disease, coronary atherosclerosis, and cardiac arrhythmia and cardiomyopathy. Although heart disease is the leading cause of death in the United States, occupational exposure to chemicals is considered less prevalent and less important than risk factors in the diet, in the environment, and in familial or inherited susceptibility to cardiovascular diseases.

Although it is relatively simple to establish a strong association between exposure to halogenated solvents and cardiac arrhythmias, it is more complex to obtain supportive evidence as to whether chemicals play a major role in coronary ischemic heart disease and atherosclerosis. Occupational heart diseases can be grouped into three major categories. These can be subgrouped according to the method of investigation, which may involve clinical studies, pathological observations, or experimental animal studies (Table I): (a) *ischemic heart disease* (Methods A, B, and C), including mortality studies, exercise testing for angina pectoris, and coronary blood flow indicators; (b) *coronary atherosclerosis* (Methods D, E, and F), demonstrable in patients by angiography and histopathology, atherosclerosis in experimental animals, and *in vitro* studies of hematologic factors; and (c) *cardiac arrhythmia and myopathy* (Methods G and H), both clinically and experimentally induced. The three groups of methods and eight subgroupings (A to H) are carried over to consideration of occupational heart disease associated with exposure to chemicals in the course of manufacturing and processing of industrial products. The chemicals supposedly associated with occupational heart diseases are listed in Table I under five classes: one inorganic and four organics. Each compound is identified by notations on investigative methods A to H.

Inorganic Oxides and Metals

Carbon monoxide is most widely discussed as a major substance in the etiology of occupational heart disease. Workplace exposure to carbon monoxide is encountered when it is generated in manufacturing an industrial product. In the steel industry, carbon monoxide is produced in blast furnace

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TABLE 1. Industrial chemicals reported to be associated with occupational heart disease.

Industrial chemicals	Ischemic heart disease	Coronary atherosclerosis	Arrhythmias and myopathy
Inorganics: oxides and metals			
Carbon monoxide*	A B C	D E F	G H
Carbon dioxide*			G
Nitrogen oxides*			G
Arsenic	A		H
Cadmium*	A		
Cobalt	A		H
Lead	A	F	
Nitrogenous compounds			
Nicotine*	A		
Aniline*		F	
Catechol*			G
Dinitrotoluene	A		
Ethylene glycol dinitrate	A C		G
Hydrazine*			G
Hydrocyanic acid*	C		H
Nitroglycerin	A C		G
Pyridine*			G
2-Toluidine*		F	
Polynuclear aromatic hydrocarbons			
Benzo[a]pyrene*	A	E	
7,12-Dimethyl (a,h) anthracene		E	
3-Methylcholanthrene		E	
Nonhalogenated solvents			
Carbon disulfide*	A B C	D E	H
Acetaldehyde*			G
Acetone*			G
Benzene*			G
Dimethylamine*			G
Methylamine*			G
Phenol*			G H
Toluene*			G
Halogenated solvents			
Methyl chloride*			G H
Methyl chloroform			G H
Methylene chloride		F	G H
Trichlorofluoromethane			G H

*Sidestream smoke (SSS) constituent.

*Metabolite carbonyl sulfide is ETS constituent.

Method A, mortality studies; Method B, exercise testing and angina pectoris; Method C, coronary blood flow indicators; Method D, coronary angiography and histopathology; Method E, atherosclerosis in experimental animals; Method F, *in vitro* hematologic factors; Method G, irregular heartbeat; Method H, experimentally induced cardiomyopathy.

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smelting of iron ore, cast welding, and vehicular production. Operators of vehicles, parking attendants, tunnel workers, car emission inspectors, tool operators, and traffic police are constantly exposed to exhaust fumes and elevated levels of carboxyhemoglobin in such workers have been reported. All eight subgroups of methods have been applied to arrive at an extensive cardiac toxicologic profile of carbon monoxide (Methods A to H in Table 1). The two other oxides and four heavy metals listed in Table 1 have been less thoroughly investigated.

Among heavy metals reportedly associated with heart disease are arsenic, cadmium, cobalt, and lead. The pathogenesis of heart disease potentially associated with workplace exposure may vary according to volatility of the metallic compound and its exposure level. Cadmium has not been reported to influence the heart directly but may be related to hypertension, which may lead to cardiac complications. Lead may influence the blood and ultimately interfere with cardiac metabolism and function. Arsenic, cobalt, and lead are cellular poisons and there are experimental heart models to support the occurrence of cardiomyopathy from these metals. Only cadmium has been detected in tobacco leaf and tobacco smoke; traces of cadmium are derived from soil.

Nitrogenous Compounds

The ten examples in this group include the following: nicotine (an alkaloid), hydrocyanic acid, and raw products for the manufacture of explosives such as ethylene glycol dinitrate and nitroglycerin. The other six examples (aniline, catechol, dinitrotoluene, hydrazine, pyridine, 2-toluidine) are necessary in the manufacture of pharmaceuticals, pesticides, and dyes. The cardiac toxicologic profiles for each of these compounds are not completely known and have been studied only by one, two, or three methods. The entry on nicotine refers to handling of tobacco leaf, such as cigar manufacturers, kiln dryers, and warehouse operators.

Polynuclear Aromatic Hydrocarbons (PAH)

These are formed as a result of pyrolysis or incomplete combustion of organic materials. There are several hundred PAHs and only a dozen have been reported to be associated with skin tumors via skin painting in mice. Benzo[a]pyrene is the most widely studied compound and only research scientists are occupationally exposed to this single PAH. Workers potentially exposed to PAH mixtures include coke oven operators, creosote wood applicators, asphalt road pavers and roofers, aluminum smelters, and diesel engine operators. Benzo[a]pyrene and two other PAHs listed in Table 1 have

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been reported to be associated with atherosclerosis in an experimental model. There are no human studies relating to heart disease other than mortality statistics of workers exposed to PAH mixtures.

Nonhalogenated Solvents

Carbon disulfide is a solvent used in the manufacture of viscose rayon, cellophane film, electronic vacuum tubes, sulfur-containing soil disinfectants, and carbon tetrachloride. This is the only solvent for which there are strong data on an association with ischemic heart disease in workers, as well as coronary atherosclerosis in experimental animals. The cardiac toxicologic profile is complete except for the lack of *in vitro* studies on hematologic factors and cardiac susceptibility to arrhythmia. The seven other solvents have not been studied for occurrence of ischemic heart disease and coronary atherosclerosis.

Halogenated Solvents

The author and his colleagues have written monographs on the cardiotoxicity of chlorinated and fluorinated solvents (5-7). Four solvents are identified in Table 1 from the original list of more than 100 solvents that are considered cardiotoxic. The four selected solvents (methyl chloride, methyl chloroform, methylene chloride, and trichlorofluoromethane) are reported to cause fatal cardiac arrhythmia and sudden death in the course of accidental industrial poisonings. Usually it cannot be proved whether cardiac arrest was caused by a direct cardiac effect or the result of respiratory paralysis and coma, since most halogenated solvents are not only cardiotoxic but also central nervous system depressants. Experimental animal studies have supported the potential role of sublethal doses of solvents in cardiac arrhythmias and myopathies, independently of coronary vessels and central nervous system involvement.

Miscellaneous Compounds

Industrial chemicals potentially related to heart disease, but which appear not to directly influence the heart, blood vessels, and circulating blood, are omitted from Table 1. Insecticides, including organophosphates, are reportedly associated with irregular heart rhythms because of their influence on the autonomic nervous system. Chronic obstructive lung disease associated with inorganic dust particles can cause cor pulmonale. Exposure to nephrotoxins, such as mercury and dyes, has been reported to lead to cardiac complications, including congestive heart failure.

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CONSTITUENTS OF ENVIRONMENTAL TOBACCO SMOKE

Environmental tobacco smoke is a diluted and aged mixture of constituents derived from either the burning end or cigarette butt: mainstream smoke inhaled from the filtered or unfiltered tip; and sidestream smoke from the lighted end. Nonsmokers sharing a workroom with smoking workers may be exposed to ETS. Sidestream smoke is not inhaled directly by nonsmokers but is diluted immediately by air in the workplace and continuously by air exchanges. The magnitudes of differences between concentrations of substances in mainstream smoke inhaled by the smoker and ETS exposure of nonsmokers have been summarized in a National Research Council monograph (8). The ranges reported in the literature (parts per million or parts per billion) are as follows:

	Mainstream Smoke	ETS
Carbon monoxide	24,900–57,400 ppm	1–18.5 ppm
Nicotine	430,000–1,080,000 ppb	0.5–7.5 ppb
Benzo[<i>a</i>]pyrene	5–11 ppb	0.0001–0.074 ppb

The dilution factors for peak values are as follows: 3100 for carbon monoxide, 144,000 for nicotine, and 148 for benzo[*a*]pyrene. There is no uniform dilution for all three because of varied levels in mainstream smoke relative to sidestream smoke. The unpredictable fates of vapor components (e.g., carbon monoxide) and particulates (e.g., nicotine and benzo[*a*]pyrene) are influenced by humidity, temperature, air movement, and adsorption by machinery and furnishings in the workplace.

Work Standards for Industrial Chemicals

The minute levels of carbon monoxide in ETS, up to 3100 times less than the concentration in mainstream smoke, pose a critical challenge to claims that ETS exposure can cause heart disease in nonsmokers. Proponents of the claimed association between ETS exposure and heart disease in general (occupational and nonoccupational) contend that three ETS constituents underlie this relationship: nicotine, carbon monoxide, and polynuclear aromatic hydrocarbons. For completeness, there are 21 reported constituents of sidestream smoke that are also used as industrial chemicals, which are sometimes discussed as potentially associated with heart disease. These are the same 21 industrial chemicals listed in the first column of Table 1 that are manufactured, processed, or emitted in workplaces and are potentially associated with heart disease (marked with superscript *a* in first

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column, Table 1). Most halogenated solvents, heavy metals, and polycyclic aromatic hydrocarbons have not been detected in ETS (no superscript in Table 1).

The list of 21 sidestream smoke constituents input to ETS in Table 2 is a revision of the author's listing of suspected pulmonary carcinogens in ETS (9,10). Also listed in Table 2 are corresponding threshold limit values (TLVs) for various substances, defined as the recommended standards for 8-hr daily exposure for the prevention of occupational disease (11). Table 2 includes a column of target organs for acute or initial exposure, as well as for chronic or long-term exposure. When TLV levels are exceeded, early and late signs of toxicity appear in skin, mucosa, lungs, liver, kidneys, blood, blood vessels, and nervous system. Manifestations of cardiotoxicity may occur either in acute lethal concentrations (more than 20 times TLV) or repeated exposure to very high, but sublethal, concentrations (more than two to five times TLV, depending on the compound).

TABLE 2. Sidestream smoke (SSS) constituents with threshold limit values (TLV)

Chemical name	Acute: chronic ^a	Max SSS (mg cig)	TLV (mg m ⁻³)	Cigarette equivalent
Nicotine	M/N	8.2	0.5	6.6
Carbon monoxide	B/N	108	55	50
Methyl chloride	M/N	0.88	10.3	1,170
Cadmium	M/P	0.0007	0.01	1,430
Acetaldehyde	M/P	1.26	180	1,430
Nitrogen oxides	M/N	2.8	50	1,780
Carbon dioxide	N/N	440	9000	2,040
Pyridine	M/H	0.39	16	4,100
Phenol	M/P	0.25	19	7,600
Hydrocyanic acid	B/N	0.11	11	10,000
Methylamine	M/N	0.1	13	13,000
Benzene	N/B	0.24	32	13,300
Catechol	D/K	0.14	23	16,500
Aniline	B/B	0.011	8	44,000
Dimethylamine	M/H	0.036	18	50,000
Carbonyl sulfide	N/V	0.0546	30 ^b	54,945
Hydrazine	M/H	0.00009	0.13	145,000
Acetone	M/N	1	1780	178,000
Benzo[a]pyrene	c	0.00009	0.2	222,000
2-Toluidine	M/B	0.003	9	300,000
Toluene	N/B	0.000035	375	1,000,000

^aTarget organs: B, blood; D, dermal; H, hepatic; K, kidney; M, mucosal; N, nervous; P, pulmonary; V, vascular.

^bMetabolite of carbon disulfide with corresponding TLV used to calculate cigarette equivalent.

^cNo TLV for benzo[a]pyrene; TLV for coal tar pitch volatiles used to calculate cigarette equivalent.

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Cigarette Equivalents to Attain TLV

The 21 sidestream smoke constituents with established workplace standards are listed in the order of increasing number of cigarette equivalents, defined as the number of cigarettes burned in a sealed enclosure of 100 m³ to attain, but not to exceed, the corresponding TLV (last column, Table 2). The list starts with nicotine, which is a reported mucosal irritant (acute exposure) and an autonomic nervous system stimulant (chronic or repeated exposure). The maximum reported sidestream smoke (SSS) collected from one burning cigarette is 8.2 mg. On the basis of TLV (0.5 mg/m³), it would take 6.6 cigarettes to attain TLV for 100 m³ in a sealed, unventilated enclosure ($0.5 \times 100 \div 8.2$). It is unlikely for the nicotine concentration in public places to attain the TLV level. If smoking has been at an extremely high level in poorly ventilated rooms, subjective discomforts would be expected to lead to corrective measures before nicotine levels would approach the TLV. The second SSS constituent listed in the order of increasing cigarette equivalents is carbon monoxide: 50 cigarettes burning in a 100 m³ sealed chamber to attain the corresponding TLV (12).

Other than nicotine and carbon monoxide, the remaining 19 SSS constituents would require more than 1000 cigarettes to attain the corresponding TLV. Such excessively high cigarette equivalents suggest that to attain TLV levels, more than 1000 cigarettes need to be ignited simultaneously in an enclosed space of 100 m³. Consideration of cigarette equivalents clearly indicates that exposure to ETS constituents in workplaces rarely approximates TLVs.

Nicotine as ETS Marker

That nicotine and its major metabolite (cotinine) are detected in blood and urine of ETS-exposed nonsmokers has been utilized by proponents of the ETS-Heart disease hypothesis. Their reasoning is as follows: since nicotine is the major cause of heart disease seen in cigarette smokers, it follows that any nicotine derived from ETS can cause heart disease in exposed nonsmokers. However, there is disagreement concerning whether any nicotine absorbed by nonsmokers can influence the heart. The estimates of ETS exposure are as follows: a nonsmoker's exposure might be, at most, the nicotine equivalent of $\frac{1}{1000}$ to $\frac{1}{10000}$ cigarette in one hr, which has not been reported to have a significant pharmacologic action. In animal experiments, inhalation, ingestion, parenteral injection, and dermal application of nicotine have been reported to influence cardiac function, coronary circulation, and atherogenesis, but these studies used amounts of nicotine that cannot be attained by ETS exposure. Furthermore, coronary atherosclerosis has not been reproduced in experimental animals by injection of nicotine. High nicotine levels of pipe smokers compared to cigarette smokers are not report-

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edly associated with an increased incidence of ischemic heart disease (13). Workers processing tobacco leaf (cigar making, leaf curing, and warehouse workers) also have not been reported to show a higher incidence of heart disease, compared to nontobacco workers (14).

Cardiac Toxicologic Profile of Industrial Chemicals

The 21 chemicals listed in Table 2, when individually used in factories below the corresponding TLV, have not been associated with heart disease nor any adverse effect on corresponding target organs, that is, mucosal surfaces, skin, blood, nervous system, lungs, kidneys, and liver (see second column of Table 2). The same 21 ETS constituents also appear in Table 1 of industrial chemicals, together with 11 industrial chemicals *not* reported to be present in ETS. As outlined in Table 1, the existing methods for establishing cardiac toxicologic profiles are as follows: Methods A, B, and C for ischemic heart disease; Methods D, E, and F for coronary atherosclerosis; and Methods G and H for cardiac arrhythmia and myopathy. Most industrial chemicals have been studied by one or two methods, thus contributing to an uncertainty of whether these 21 chemicals are related to heart disease. Those that have been studied by three to eight methods have a stronger basis for claims of a relationship with occupational heart disease, namely, carbon monoxide, ethylene glycol dinitrate, nitroglycerin, carbon disulfide, and methylene chloride. There are review articles on industrial chemicals reportedly associated with heart disease (15-17).

A principal objective of this chapter is to evaluate the potential relationships between occupational chemicals and heart disease, in terms of the extent of the available data from human studies and animal experiments. There are reviews on individual industrial chemicals and the occurrence of diseases not limited to the heart (11,18,19). A standard source of reference is the Registry for Toxic Effects of Chemical Substances available in hard copy (20) as well as on-line in the TOXNET database updated by the National Library of Medicine and National Institute of Occupational Safety and Health. Textbooks on internal medicine and cardiology do not have special chapters devoted to occupational heart diseases so that it has been difficult to interest the medical profession. Because industrial chemicals are potentially associated with heart disease by the inhalational route, a World Health Organization monograph entitled *Air Quality Guidelines for Europe* (21) is a helpful reference source. It discusses the following industrial chemicals in a uniform format: inorganic oxides such as carbon monoxide and nitrogen dioxide; heavy metals such as arsenic, cadmium, and lead; polynuclear aromatic hydrocarbons such as benzo[*a*]pyrene; nonhalogenated solvents such as benzene, carbon disulfide, and toluene; and halogenated solvents such as methyl chloroform and methylene chloride. These 11 industrial chemicals identify those that have been measured indoors (workplace envi-

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ronment) but also emitted outdoors into the environment. Ischemic heart disease is mentioned under carbon monoxide and carbon disulfide.

ISCHEMIC HEART DISEASE

Ischemic heart disease is represented clinically by angina pectoris, myocardial infarction, cardiac arrhythmia, cardiogenic shock, and sudden death. The epidemiologic and clinical literature on work-associated ischemic heart disease consists of the following: Method A, mortality statistics; Method B, exercise testing for anginal pain; and Method C, coronary blood flow indicators. The plan is to state how each method has been applied to the concept that ischemic heart disease is related to exposure to chemical substances in the manufacture of industrial products. Although ETS levels are unlikely to attain their corresponding TLV, it is important to discuss the existing claim that the mere presence of these chemicals is sufficient to suggest an association between ETS and occupational heart disease.

Method A: Mortality Studies

There are scant data on heart disease in workers differentiated by exposure or nonexposure to ETS in the workplace. Most published studies relate to differences in spousal smoking habits, based on the premise that mortality rates of nonsmokers might be influenced by smoking habits of their spouses. In 1984, Schievelbein and Richter (22) reviewed the available literature and concluded that in concentrations of carbon monoxide and nicotine reportedly present in ETS, it is unlikely for ETS exposure to play any role in the development and progression of ischemic heart disease. The 1986 Reports of the Surgeon General and the National Research Council, after examining the available information, concluded that further studies on the potential relationship between ETS exposure and cardiovascular disease are needed in order to determine whether ETS increases the risk of cardiovascular disease in general, and of ischemic heart disease in particular (8,23). Recent epidemiologic studies were reviewed by Wexler (4), who questioned the reported relationship between household exposure to ETS and heart disease.

Prospective (cohort) and retrospective (case control) studies have been conducted on the potential relationship between ETS exposure and IHD incidence. Although some spousal studies (smoker married to nonsmoker) report a statistically significant association, most studies do not. Lee and his collaborators (24) conducted studies in England consisting of administering a questionnaire to 200 hospital patients and 200 controls for each gender and age group. Patients with ischemic heart disease and controls did not show any statistically significant difference in ETS exposure based on smoking habits of spouses. Exposure to ETS was also evaluated by an index of pres-

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ence in the workplace, during travel, and at leisure. From the standpoint of worker ETS exposure, the negative results of Lee et al. (24) are more relevant than positive results of spousal studies that do not include ETS exposure outside the home environment.

Carbon Monoxide

Heart disease mortality rates have been reported for workers exposed to high levels of carbon monoxide from vehicular emissions (tunnel workers, bus drivers, parking attendants) and industrial furnaces (steel foundry, coke oven, chemical manufacture) (25,26). However, the results of occupational exposure to high levels of carbon monoxide do not support the argument that this substance contributes to heart disease associated with ETS exposure, in which reported levels of the gas are a tiny fraction of the TLV.

Carbon Disulfide/Carbonyl Sulfide

These two compounds are linked by the fact that the former is an industrial chemical reported to be associated with heart disease among workers producing viscose rayon fibers. This compound is metabolized to carbonyl sulfide, which happens to be a reported SSS constituent. The concentration of carbonyl sulfide is so low that it is unlikely to attain the TLV (Table 2: 54,945 cigarettes to attain TLV). However, it is important to discuss mortality studies of rayon viscose workers, because other than carbon monoxide, carbon disulfide is the only industrial chemical for which there are extensive data on an association with ischemic heart disease. In a critical review of the toxicologic literature on carbon disulfide, Beauchamp et al. (27) reviewed data on the mortality rates of viscose rayon workers. In Finland, where there is a high incidence of ischemic heart disease, a significantly higher mortality rate has been reported among exposed workers compared to a control group. However, in Japan where there is a notably lower incidence of ischemic heart disease, no increased mortality rate has been reported among viscose rayon workers. The excess deaths attributed to carbon disulfide became apparent if predisposing risk factors existed, such as hypertension, hyperlipidemia, and excessive intake of cholesterol and saturated fats (27,28).

The above observations are essential to consider in attempts to interpret mortality studies on ETS exposure. Dietary intakes of cholesterol and fatty food were not considered as a confounding factor in mortality studies relating to workers exposed to the industrial chemicals listed in Table 1 (with Method A notation). The reported higher susceptibility of Scandinavians to heart disease is reflected by the lower TLV (15 mg/m³) compared to the TLV in other European countries and the United States (30 mg/m³) (18,19).

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Polycyclic Aromatic Hydrocarbons (PAH)

It has been suggested by proponents of the ETS-heart disease hypothesis that Scandinavian roofers show excess mortality for ischemic heart disease (3). They extrapolate from PAH-exposed roofers to ETS-exposed workers without recognizing the difference in composition of PAH. Exposures to PAH among coke oven workers, creosote wood appliers, and asphalt road builders have not been reported to be associated with excess mortality for heart disease but have been reported to be associated with excess mortality for lung cancer. From the standpoint of chemical composition of PAH exposures determined by nature of product, PAH exposures of roofers are irrelevant to ETS exposure (see also Method F).

Heavy Metals

Mortality studies on work-related exposure have been reviewed by Kristensen (16). Lead and cadmium workers have been reported to show a higher mortality rate from heart disease and hypertension. In the absence of experimental animal studies, heart disease is likely to be a complication of hypertension rather than a direct effect of lead or cadmium on the heart and coronary vessels. The suggestion that heart disease may be associated with workplace exposure to arsenic or cobalt can be traced to instances of beer drinking contaminated with either of these metals, and subsequent death from cardiomyopathy.

Method B: Exercise Testing and Angina Pectoris

Exercise testing is essential for the diagnosis of ischemic heart disease (29). A positive diagnosis is based on the appearance of chest pain or classical angina pectoris after completion of standardized exercise on a treadmill or bicycle ergometer. Exercise testing has also been used to evaluate severity of arteriosclerotic heart disease based on time of onset of an ischemic pattern in the electrocardiogram as well as the appearance of cardiac arrhythmias.

ETS Exposure of Anginal Patients

All available reports on exercise testing do not relate to specific occupational groups comparing two subgroups: with ETS exposure and no ETS exposure. There are two studies on anginal patients that suggested to the investigators that ETS exposure during bicycle ergometry may shorten the time period to onset of chest pain. The first study, reported in 1978, consisted of a group of ten American male veterans (30). For various reasons,

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the 1978 protocol for exercise testing was evaluated by an ad hoc committee of the Environmental Protection Agency. In 1983, the committee concluded that the method used on American male veterans "did not meet a reasonable standard of scientific quality" (31). In 1987, a second study of exercise testing during ETS exposure was reported by Soviet investigators (32). The results were essentially similar to those reported from American veterans. It is this author's opinion that shortening onset of anginal pain during exercise testing as a result of ETS exposure has not been proved pending evaluation of the Soviet protocol. Anti-anginal drugs sold in the United States are supported by results of exercise testing in European laboratories that have been approved by the U.S. Food and Drug Administration and so far, the list does not include any Soviet laboratories.

Influence of Carbon Monoxide on Exercise Testing

Proponents of the theory that ETS exposure aggravates angina pectoris emphasize the presence of carbon monoxide in ETS, in spite of the fact that the concentration inhaled is 3100 times lower than mainstream smoke. Blood carboxyhemoglobin levels of subjects exposed to ETS in public places range from 1 to 3% among nonsmokers. Slight elevations of blood carboxyhemoglobin level (to 2 and 3.9%) have been reported following administration of carbon monoxide in air (100 and 230 mg/m³) (33). Exercise testing of heart disease patients was reported to result in an ischemic pattern of electrocardiogram at these blood carboxyhemoglobin levels. However, as indicated in Table 2, this would require more than 100 and 200 cigarettes burning in a sealed enclosure of 100 m³ for carbon monoxide to attain about 2 and 4 times the TLV, respectively.

ETS Exposure as Risk Factor for Angina Pectoris

Proponents of the claim that ETS exposure aggravates angina pectoris have not considered the complexities of the disease separate from other manifestations or complications of ischemic heart disease (i.e., acute myocardial infarction and sudden deaths). Although prospective and retrospective studies report that cigarette smoking is one of many risk factors for acute myocardial infarction and sudden deaths, the data on angina pectoris are even more complex. The 1983 report of the Surgeon General on cardiovascular disease, referring to risk factors, concluded that "variation in the strength of association between smoking and angina pectoris may be influenced by . . . methodological considerations" (ref. 34, p. 70). More recently, it has been argued that the 30-year results of an ongoing prospective study at Framingham, Massachusetts, indicate that cigarette smoking is a negative risk factor in women (i.e., incidence lower in women smokers compared to

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women nonsmokers) (35). The results in men have indicated either a positive or no significant relationship between cigarette smoking and angina pectoris, depending on methodological variation. Some studies relating to cardiac patients admitted to hospitals report that after an initial cardiac episode, the prognosis is not influenced by smoking (36,37). After the initial infarction, prior smoking was not associated with the severity of subsequent complications. These observations on cigarette smoking in relation to the prognosis of myocardial infarction and the influence of angina pectoris raise additional questions. How can ETS, a dilute mixture of tobacco smoke components in air, aggravate angina pectoris or influence the prognosis of acute myocardial infarction, in light of recent inconsistencies in data derived from smokers?

Method C: Coronary Blood Flow Indicators

Coronary arteries visualized by angiography can show obstruction that is organic (arteriosclerosis and thrombosis) or nonorganic (vasospasm) in nature. Total coronary blood flow is measured by a tracer clearance technique. Patients with ischemic heart disease show a reduction in coronary blood flow that is limited to an infarcted area. When infarction is detected in workers previously exposed to carbon monoxide or carbon disulfide, it is not possible to isolate the potential association with chemical exposure from other potentially confounding risk factors. Carbon monoxide alone, by increasing carboxyhemoglobin, can increase coronary blood flow; but the result would be an oversupply of blood without reduced oxygen utilization because of poisoning oxidative enzymes. Myocardial metabolism requires the sampling of blood from the coronary sinus and a systemic artery to obtain arteriovenous differences of oxygen, carbon dioxide, lipoproteins, and glucose metabolites. There are more direct methods for measuring coronary blood flow in experimental animals (dog, cat, pig, monkey). The relative importance of metabolic and neurohumoral control has been evaluated in experimental animals [see reference cited by Bove (38)]. It has not been possible to reproduce coronary heart disease by exposure to tobacco smoke, which contains nicotine levels higher than ETS, so it is doubtful that existing animal models can give positive results from ETS exposure.

Nitroglycerin and organic nitrates are useful vasodilators for the relief of angina pectoris. The pharmacologic action of nitroglycerin is manifested in workers who are exposed daily to nitroglycerin and ethylene glycol dinitrate, but after a weekend of nonexposure, develop chest pain on Monday morning. Workers suffer from vasospastic angina as a result of nitrate withdrawal during the weekend and are relieved upon resuming nitrate work exposure. Autopsied workers did not show coronary arterial obstruction, confirming the occurrence of vasospastic angina brought about by weekend withdrawal from nitrate. Workers were acclimatized to the nitrate level in work environment (14-16).

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CORONARY ATHEROSCLEROSIS

The term coronary *atherosclerosis* used in this chapter refers to histopathologic changes in arteries leading to *ischemic heart disease* (see preceding section). Although both terms are included in *coronary heart disease*, there are differences in methodology. This section is devoted to progressive organic lesions of coronary arteries, the methods for detection, and their evolution, based on human observations and animal experimentation. The focus is on industrial exposure to carbon disulfide and carbon monoxide, because of the relatively greater amounts of data on these substances. The potential relevance of these industrial chemicals to ETS exposure is also discussed.

The demonstration of coronary atherosclerosis ideally should include histopathologic evidence derived from autopsy (Method D). This has been accomplished for worker exposure to carbon disulfide, which has been supported by the occurrence of hyperlipidemia in exposed workers and coronary atherosclerosis in experimental animals (Method E). On the other hand, some industrial chemicals are associated with the development of coronary atherosclerosis based on animal experiments only or on hematologic changes in workers that in animals contribute to aortic atherogenesis (see entries in Table 1). Some of these observations have been used to support the claim that ETS exposure is involved in coronary atherosclerosis. A distinction is made between concepts derived from human studies (Method D), animal experiments (Method E), and *in vitro* techniques (Method F).

Method D: Coronary Angiography and Histopathology

The most direct method for diagnosis of coronary atherosclerosis is by histopathologic examination and coronary angiogram. Although there are isolated reports that workers exposed to carbon monoxide suffer from increased coronary atherosclerosis (antemortem or postmortem), this exposure is confounded by competing risk factors such as personal habits, familial history, and environmental pollution. Among viscose rayon workers, the occurrence of coronary atherosclerosis reported at autopsy of workers dying of heart disease led to mortality studies (Method A). Workers are also reported to suffer from hyperlipidemia, which is not entirely due to carbon disulfide exposure. It is difficult to replicate earlier studies on workers using modern techniques of diagnosing coronary atherosclerosis, because exposure levels have come under strict regulation.

There are no case reports of coronary atherosclerosis in workers exposed to a single polynuclear aromatic amine because workplace exposure is to mixtures that include benzo[*a*]pyrene. Only research laboratory workers investigating benzo[*a*]pyrene are candidates for long-term exposure, and so far there has been no report of a higher incidence of heart disease. There are

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also no case reports of coronary atherosclerosis from prolonged exposure to the heavy metals and nitrogenous compounds listed in Table 1.

Method E: Coronary Atherosclerosis in Experimental Animals

Repeated attempts to induce coronary atherosclerosis in experimental animals by inhalation of cigarette smoke have failed. Additional feeding with a cholesterol-enriched diet has reportedly led to the development of atherosclerosis not involving coronary arteries. In baboons, after 2–3 years of oral feeding of cholesterol and saturated fat, and daily inhalation of cigarette smoke, arterial lesions were compared between smokers and controls. Among male baboons, the extent of carotid atherosclerosis was greater in smokers than in controls, but there were no significant differences in atherosclerosis of the aorta, coronary arteries, iliac-femoral, and bronchial arteries. Among female baboons, there were no significant differences in atherosclerosis between smokers and controls (39).

The same general remarks apply to experimental testing of carbon monoxide in levels far exceeding those reported for ETS exposure. Rabbits, pigeons, and chickens are reported to need supplementary feeding of cholesterol to show carbon monoxide-induced aortic atherosclerosis (40).

Carbon disulfide is the only industrial chemical reported to cause atherosclerosis in animals without supplemental cholesterol feeding. Coronary and aortic atherosclerosis and myocardial lesions were detected in rats after 4 months of inhalation exposure (28). There were elevations of serum cholesterol, phospholipid, and triglycerides, indicating similarity to the human form of atherosclerosis. Other investigators have tested carbon monoxide and benzo[*a*]pyrene and have not observed hyperlipidemia and atherosclerosis similar to those reported for carbon disulfide. In the past, research on carbon monoxide, benzo[*a*]pyrene, and other polynuclear aromatic hydrocarbons has not been directed to a comparison with carbon disulfide.

Polynuclear aromatic hydrocarbons have been reported to induce aortic atherosclerosis in pigeons and chickens (41–44). It has been speculated that these studies in birds relate to human subjects exposed to ETS (2). There are several reasons for the inapplicability of results of these bird experiments to coronary atherosclerosis: (a) 7,12-dimethylbenzo[*a,h*]anthracene and 3-methylcholanthrene are not known to be present in ETS; (b) although benzo[*a*]pyrene is reportedly present in ETS, the dose administered, 50 mg/kg injection, is far fetched compared to concentration levels in SSS, which is 0.00009 mg/cigarette; (c) hepatic metabolism is essential for atherogenesis in one strain, but not in the other strain, a sequence that applies to oral or injected compounds but not to the inhalation route; and (d) the typical result is aortic atherosclerosis and rarely coronary atherosclerosis. Aortic atherosclerosis is different from coronary atherosclerosis because of myocardial extravascular support in the latter. There are intracardiac mechanisms that influence coronary circulation, which are absent in other arterial beds.

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There are long-term animal experiments designed to study carcinogenicity or polynuclear aromatic hydrocarbons and, so far, coronary atherosclerosis has not been reported in sacrificed animals.

Method F: *In Vitro* Studies of Hematologic Factors

Hematologic factors include alterations in hemoglobin oxygen transport such as carbon monoxide and methylene chloride increasing carboxyhemoglobin; and aniline and 2-toluidine leading to methemoglobinemia. The ultimate consequence is a reduced supply of oxygen and presumably atherosclerosis resulting from carbon monoxide. However, prolonged testing with methylene chloride or aniline has not been reported to produce experimental atherosclerosis, suggesting that these two industrial chemicals reduce hemoglobin oxygen transport differently from carbon monoxide.

Several techniques have been developed for the specific purpose of discovering therapeutic agents for the prevention, suppression, and reversal of atherosclerosis. Drugs for influencing blood platelets, blood lipoprotein levels, and endothelial vulnerability evolved from application of *in vitro* testing of blood derived from patients with ischemic heart disease, as well as peripheral vascular diseases. The same techniques for identifying therapeutic agents have also been applied to investigating how carbon monoxide and ETS might play a role in atherosclerosis. The interpretation of results derived from one test has been extended to include the entire progression of atherosclerosis even though the test was intended to show a therapeutic, rather than toxic, effect of chemical agents.

In vitro tests have been applied to blood from ETS-exposed subjects, based on the assumption that any reported effect will contribute to coronary atherosclerosis. It should be pointed out that chemically induced platelet aggregation leads to vascular clot formation, which does not necessarily involve interaction with endothelial cells and the formation of atherosclerotic plaque. Also, in the laboratory, it has not been possible to initiate aortic plaque formation by exceeding the normal level of fibrinogen. Any reported increase in fibrinogen level in the blood of ETS-exposed subjects may not be relevant to a potential relationship with coronary atherogenesis. It is conceivable that, for some people, ETS exposure may be perceived as stressful, with release of catecholamines, and that catecholamines are responsible for *in vitro* testing results. It has not been possible to conduct a double-blind testing of ETS exposure since both investigator and subject can detect ETS presence.

Platelet Aggregation

Exposure of healthy nonsmokers to ETS is alleged to alter results of *in vitro* testing of platelets in platelet-rich plasma. Aggregation of platelets is

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tested by the following agents added *in vitro*: edetic acid and formaldehyde or prostaglandin. The possibility that ETS exposure increases platelet aggregation is alleged to be an important step in the evolution of coronary atherosclerosis in nonsmokers (2).

In vitro studies of platelet aggregation in blood derived from smokers have reported inconsistent results, which question the applicability of this method to ETS exposure in nonsmokers. Platelet aggregation testing using whole blood reported no statistically significant differences between nonsmokers and smokers (45). Cigarette smoking is reportedly associated with alterations in platelet factors involved in thrombus formation, but the change has been attributed to the presence of carbon monoxide levels higher than those reported in subjects exposed to ETS (46). *In vitro* testing does not necessarily reflect events *in vivo*. Although platelets may be activated *in vivo*, they become attached to erythrocytes or form platelet aggregates during the collection and centrifugation needed to make platelet-rich plasma. There is some evidence that activated platelets are lost from supernatant "platelet-rich plasma," which includes older or less active platelets.

Plasma Fibrinogen Levels

Another *in vitro* test for a clotting factor has been added to the list of reports supporting the ETS-heart disease hypothesis. Patients with ischemic heart disease were questioned about their smoking habits, and nonsmokers were queried for ETS exposure in the workplace and household. Control subjects were derived from the same community in Australia (47). It was reported that the collected blood samples showed higher fibrinogen concentrations among current smokers than nonsmokers. Subjects exposed to ETS had higher levels than those not exposed. The differences were not statistically significant because of the high variability of measured fibrinogen levels. According to the questionnaire responses, levels of ETS exposure at work were reported to be higher than at home, but the estimated odds ratio for heart disease was less than one. The investigators interpreted their results to indicate inaccurate reporting of ETS exposure or the possibility that household exposure to ETS is associated more with heart disease than is workplace exposure. The potential relevance of fibrinogen levels in relation to ETS exposure is further questioned by observations that psychosocial factors may influence the plasma fibrinogen concentration in patients with ischemic heart disease (48).

CARDIAC ARRHYTHMIA AND MYOPATHY

The third and last group of methods for establishing cardiac toxicologic profiles for industrial chemicals relates to alterations in cardiac function.

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The methods are intended to detect irregularities in heart beat or rhythm, to measure excitability of the intact heart, and to record electrical properties of excised atrium and papillary muscle. Cardiac output is measured by the tracer dilution technique and ventricular imaging in patients; invasive procedures are required for application of the Fick principle in patients and insertion of blood flow recorders in experimental animals. Perfusion of the excised heart offers an opportunity of measuring myocardial contractility and metabolism. Enzymatic studies and electron microscopy complete the techniques for detecting cardiomyopathy. All these procedures have been applied to determine the occurrence and mechanism for two groups of diseases: irregular heart beat or arrhythmia, and cardiomyopathy.

Method G: Irregular Heart Beat

Industrial chemical poisoning can be manifested by irregularities of heart beat or cardiac arrhythmia, in the order of increasing severity: ranging from tachycardia or bradycardia, atrioventricular block, atrial or ventricular extrasystole, atrial fibrillation, to ventricular fibrillation and cardiac arrest. The benign forms (up to atrial fibrillation) are reversible by stopping chemical exposure, but ventricular fibrillation and cardiac arrest require heroic efforts. Poisonings characterized by cardiac arrhythmias have been reported for the following (see Table 1, Method G): most halogenated and nonhalogenated solvents, some nitrogenous compounds, one heavy metal (lead), and one oxide (carbon monoxide). The arrhythmia results from a direct action of the chemical on the heart, specifically by altering excitability, conduction, and refractoriness of one or more of the following: atrial muscle, atrioventricular node, conducting system, and ventricular muscle. The effects have been reported in appropriate human studies and animal experimentation. The occurrence of poisoning by industrial chemicals does not support the proposition that since the same chemicals may be reported at minute levels in ETS, then ETS also may lead to the development of heart disease in workers.

Method H: Experimentally Induced Cardiomyopathy

The most extreme example of unjustified application of results from animal experiments to ETS exposure of nonsmokers is as follows: in the course of attempting to determine whether long-term cigarette smoking leads to cardiomyopathy, rabbits were exposed in an infant incubator (49). It was reported that all the smoke from three burning cigarettes entered the inlet of the incubator through a mechanical device and rabbits were kept for 30 min. This description appears to this author as a sealed chamber with cigarette smoke entering the inlet for 30-min periods. Several groups of rabbits were

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sacrificed: controls, after one 30-min exposure, twice daily exposure for 2 weeks, and twice daily exposure for 8 weeks. The heart was studied for mitochondrial oxidative processes. There was a decrease in respiration as well as in phosphorylation rate that was interpreted by the investigators as cardiomyopathy. The investigators recognized that carbon monoxide in the incubator was probably responsible for metabolic changes but they did not monitor air or blood levels.

Hugod and collaborators (50-52) exposed rabbits to one of the following mixtures: carbon monoxide 220 mg/m³ or four times TLV; carbonyl sulfide 130 mg/m³ or five times TLV; nitric oxide 6 mg/m³ or one-fifth the TLV. The rabbits were in air-tight exposure chambers containing freely flowing air or predetermined mixtures in air for periods ranging from 1 to 7 weeks. The results of 140 rabbits sacrificed for electron microscopic examination performed blindly, showed no morphological signs of myocardial damage. The four vapor constituents, in levels far exceeding ETS levels, were not associated with ultrastructural changes in rabbit heart, signifying the absence of cardiomyopathy.

The rabbit exposure studies described above were extended to include biochemical and histomorphologic investigation of atherosclerosis. Exposure to each of the four gas-air mixtures was not related to intimal damage of the aorta and coronary arteries. The negative results noted for carbonyl sulfide exposed rabbits do not support the claim that this known metabolite for carbon disulfide is responsible for coronary atherosclerosis reported by other investigators.

Cardiomyopathy has been reported following exposure to halogenated solvents, based on case reports of poisoning and experimental studies on intact and perfused heart. Cardiomyopathy from heavy metals is described in case reports of individuals drinking beer from containers that leached arsenic, cadmium, or lead (16). Cardiomyopathy from hydrocyanic acid is also based on case reports of poisoning and is readily supported by biochemical studies of heart muscle. Carbon monoxide is probably the most frequently encountered industrial and household chemical associated with death by cardiomyopathy. History of exposure to vehicular emissions or household natural gas is verifiable by blood analysis for carboxyhemoglobin. Among nonhalogenated solvents, only phenol has been reportedly related to cardiomyopathy (16).

CONCLUDING REMARKS

Among more than 32 industrial chemicals potentially related to heart disease, only four substances or chemical classes have extensive supportive evidence: carbon monoxide, carbon disulfide, ethylene glycol dinitrate and organic nitrates, and methylene chloride and halogenated solvents. The ef-

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fects of other industrial chemicals (oxides, nonhalogenated solvents, nitrogenous compounds, and heavy metals) have not been adequately supported by human studies and animal experiments.

Methylene chloride is a solvent prototype for industrial chemicals that may be related to cardiac arrhythmia and myopathy in lethal or sublethal levels. Carbon disulfide is a selected prototype for industrial chemicals that may be related to ischemic heart disease or coronary atherosclerosis. There are no data indicating whether prolonged exposure to low levels of methylene chloride is associated with ischemic heart disease or whether high levels of carbon disulfide are associated with cardiac arrhythmia and myopathy. Methods to establish a cardiac toxicologic profile applied to one prototype need to be applied to the other.

The cardiac toxicologic profile for carbon disulfide is as follows: (A) mortality studies of viscose rayon workers report excess ischemic heart disease deaths, provided predisposing or other risk factors are present; (B) there is a high incidence of angina pectoris reported in workers exposed to carbon disulfide; (C) there is a reduction in coronary blood flow reported in workers developing ischemic heart disease, but there are no published results of myocardial tracer clearance studies; (D) coronary angiogram and postmortem histopathologic studies report coronary atherosclerosis associated with carbon disulfide exposure; (E) coronary atherosclerosis developed in experimental animals exposed to carbon disulfide, with or without dietary cholesterol supplement. There is no information for (F) *in vitro* hematologic factors and (G) cardiac arrhythmia; (H) experimental cardiomyopathy was reportedly not detected by electron microscopy in animals exposed to five times TLV for carbon disulfide.

The cardiac toxicologic profiles for carbon disulfide and ETS are compared in Table 3. There are no comparative studies on workers with and without ETS exposures. The theory that ETS causes ischemic heart disease is based on inferences from the following: (A) epidemiologic studies of household exposures reported for nonsmoking spouses of smokers; (B) exercise studies of anginal patients with ETS exposure, but questionable protocol; (C) coronary blood flow assumed to be insufficient because carbon monoxide present in ETS; (D) coronary atherosclerosis assumed to occur because aortic atherosclerosis reported in animals exposed to carbon monoxide at considerably higher levels than ETS; (E) coronary atherosclerosis supposedly occurs because benzo[a]pyrene reportedly associated with atherosclerosis in cholesterol-fed birds; (F) *in vitro* testing for platelet aggregation and reduced fibrinogen level, suggesting atheromatous plaque formation; (G) cardiac arrhythmia postulated based on ventricular excitability studies of animals exposed to carbon monoxide; and (H) cardiomyopathy inferred from rabbit heart mitochondrial studies.

It is the opinion of this author that the available studies do not support a judgment that ETS exposure is associated with any form of occupation-re-

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TABLE 3. Cardiac toxicologic profile for carbon disulfide and environmental tobacco smoke

Method	Carbon disulfide	Environmental tobacco smoke (ETS)
Ischemic heart disease		
A. Mortality studies	Excess ischemic heart disease deaths among rayon viscose workers provided predisposing factors present	No information on workers exposed to ETS
B. Exercise testing and angina pectoris	Higher incidence of angina in rayon viscose workers; exercise testing protocol must meet U.S. agency standards	Anginal patients have shorter time to pain onset when exposed to ETS; cigarette smoking questionable risk factor in angina patients
C. Coronary blood flow indicators	Reduced coronary blood flow in patients with ischemic heart disease	
Coronary atherosclerosis		
D. Coronary angiography and histopathology		
E. Atherosclerosis in experimental animals	Coronary atherosclerosis in rats without cholesterol feeding	Polynuclear aromatic amines causing aortic atherosclerosis in cholesterol-fed birds
F. <i>In vitro</i> hematologic factors	No information	Platelet aggregation, endothelial cell damage and reduced fibrinogen level
Cardiac arrhythmia and myopathy		
G. Irregular heart beat	No information	Ventricle excitability studies of animals exposed to carbon monoxide
H. Experimentally induced cardiomyopathy	No ultrastructural changes in rabbit heart	Heart mitochondria studies from rabbits exposed to ETS

lated heart disease. Although ETS reportedly contains constituents that have been associated with occupational heart disease, the concentrations are so low that it is unlikely for any substance to attain the corresponding TLV in a work environment.

Carbon disulfide can be used as a reference model for testing whether an industrial chemical can be considered as an etiologic factor in ischemic heart disease and coronary atherosclerosis. The most comprehensive and critical review of carbon disulfide has been written by members of the Chemical Industry Institute of Toxicology. The theory that ETS exposure causes heart disease was recently summarized by university scientists who have dismissed valid criticisms as industry-supported. All research results, including industry-funded sources, should be used in evaluating the role of ETS in heart disease.

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In: Quality of the Indoor Environment

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PASSIVE SMOKING AND CORONARY ARTERY DISEASE. BIOLOGICAL PLAUSIBILITY AND SEVERITY OF EFFECT

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ABSTRACT

A number of small pieces of incriminating evidence, apparently pointing in the same direction, do not necessarily prove a crime. Therefore, before reviewing the various mechanisms suggested to incriminate ETS in CHD incidence, a brief reminder of what is actually well known about the atherosclerosis process is necessary. We shall stress what progress has been made over the last decade and what risk factors are now being considered. The role of active smoking, which has long been set in evidence by epidemiologic studies, is now fairly well understood scientifically. The mechanisms of cardio-vascular attack are triggered by two primary stimuli: nicotine and carbon monoxide. Induced effects on catecholamines, platelets, carboxyhemoglobin, fibrinogen, lipoprotein metabolism, etc... help understand their incidence on CHD. Everything however, is not altogether clear nor consistent. Concerning ETS, the ten epidemiologic studies investigating its association with heart disease mortality, produce mean RR values ranging from 1.2 to 1.4 in both sexes (Glantz). This fact and corresponding criticisms will not be dealt with here. We shall however concentrate on a detailed study of the mechanisms suggested to explain the effects of passive smoking and compare them with those of active smoking. If ETS brings into an exposed non-smoker's blood such primary stimuli as nicotine, CO, benzene, PAH allow the biological plausibility of CHD attack, but careful consideration of their mode of action and magnitude cannot, as far as is known, incriminate ETS as the third cause of mortality (Wells).

INTRODUCTION

There are now 10 epidemiological studies [1-10] on the relationship between exposure to environmental tobacco smoke (ETS) in the home and the risk of coronary heart disease (CHD) (table 1). Most of these studies have reported relative risks greater than 1.0.

(based on a presentation made by an international author in priority meeting
in Athens in April, 1992)

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Table 1. Relative risks for heart disease death from passive smoking epidemiologic studies.

Author	Type	Total cases	Relative risk	95 % confidence interval	Country
Females					
Hirayama (1984)	P	494	1.2	0.9-1.4	Japan
Gillis <i>et al.</i> (1984)	P	21	3.6	0.9-13.8	Scotland
Garland <i>et al.</i> (1985)	P	19	2.7	0.9-13.6	California
Lee <i>et al.</i> (1986)	C	77	0.9	0.5-1.6	United Kingdom
Helsing <i>et al.</i> (1988)	P	988	1.2	1.1-1.4	Maryland
He (1989)	C	34	1.5	1.3-1.8	China
Humble <i>et al.</i> (1990)	P	76	1.6	1.0-2.6	Georgia
Butler (1990)	P	64	1.4	0.5-3.8	California
Males					
Gillis <i>et al.</i> (1984)	P	32	1.3	0.7-2.6	Scotland
Lee <i>et al.</i> (1986)	C	41	1.2	0.5-2.6	United Kingdom
Svendsen <i>et al.</i> (1987)	P	13	2.1	0.7-6.5	United States
Helsing <i>et al.</i> (1988)	P	370	1.3	1.1-1.6	Maryland
Both sexes combined					
Hole <i>et al.</i> (1989)	P	84	2.0	1.2-3.4	Scotland

CHD : Coronary Heart Disease P : Prospective cohort C : Case control studies

In spite of large differences in study design and type of heart disease considered (ischaemic heart disease, death of any origin, myocardial infarction death, non fatal coronary symptoms including angina), all results have been pooled giving an overall relative risk estimate of 1.23 (limits 1.1-1.4) for 6 studies in women and 1.31 (limits 1.1-1.6) for 4 studies in men (Wells, [11]). When these values are used to calculate CHD mortality rate in the USA, they give the very high figure of 32,000 deaths/year [11].

Glantz [12] takes up this figure and collects evidence from a number of more or less relevant studies all tending to prove that this finding is plausible.

We shall first consider the formation process of atherosclerosis. It is a complex, multifactorial slowly developing phenomenon. It is therefore biologically plausible that ETS exposure may cause some blood factors to vary and accelerate the atherosclerosis process. It remains to be proven, however, that the amplitude of such variations occurring during actual ETS exposure produces an effect leading to a 30 % risk increase [12]. That is why, after a brief reminder of what is known to date about the mechanism of atherosclerosis, we shall examine what are the aggravating factors due to active tobacco smoking. Then, we shall attempt to evaluate the impact of ETS induced stimuli compared to those affecting an active smoker who is also passively exposed to his own smoke and that of other smokers.

OVERVIEW ON THE MECHANISM

Epidemiologic studies from a variety of countries throughout the world have clearly established a relationship between the development and/or the progression of atherosclerotic process and many lifestyle factors: sedentarity, obesity, dietary intake (excess calories, saturated fat, salt...), cholesterol, stress, cigarette smoking... etc.

Risk factors

Since Framingham and his team published their findings 15 years ago [13], it has been known that the three major CHD risk factors are: hypercholesterolemia, high blood pressure and cigarette smoking (Fig. 1) [14]. Combination of two or three of such risk factors has been found to increase CHD incidence nine times for two and 16 times for three factors [14].

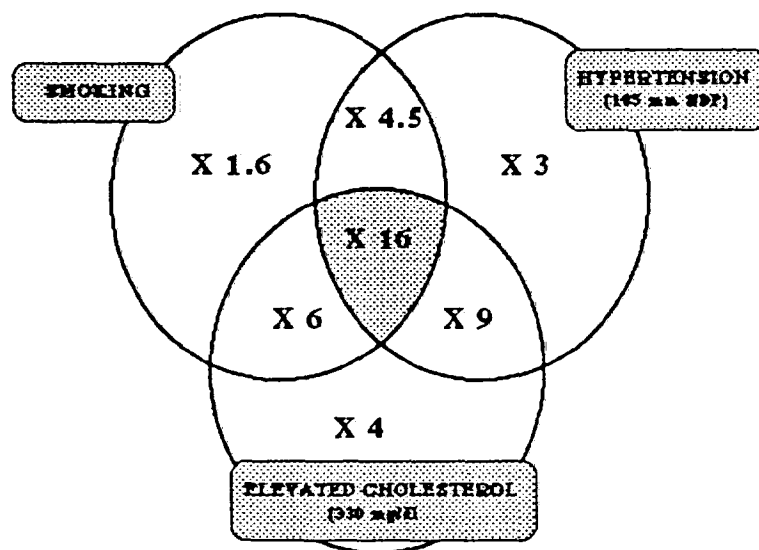


Figure 1. Increase in risk of coronary heart disease as a result of smoking, hypertension and hypercholesterolemia, relative to a 45-year-old non-smoking man with a systolic blood pressure (SBP) of 110 mm Hg and total cholesterol of 185 mg dl⁻¹. Drawing made on the basis of data from the Framingham study (from Kannel W.B. [14]).

It is now known that some of these factors should be better defined. With cholesterol, for instance, it is the hyperlipoproteinemic anomaly which must be considered (table 2). Cholesterol carriers such as LDL (Low Density Lipoprotein) represent a risk and VLDL (Very Low Density Lipoprotein) an additional risk whereas HDL (High Density Lipoprotein) counters the risk. Apolipoproteins are better correlated with CHD risk: Apo B100 (contained in LDL - VLDL) represent the risk, whereas Apo A1 (contained in HDL) counters the risk [15]. Bloodstream lipoprotein particles (16) now appear to be even more related to CHD risk. LpB or Lp(a+) [17] represent the risk whereas Lp A1 are the protecting agents [16]. These factors are generally of the genetic risk type, whereas LDL modified (18) by oxidation, acetylation, glycosylation and MDA LDL conjugation with MDA (Malondialdehyde) are due to metabolic and environmental chemical alterations [19,20]. Destruction of modified LDL by the "scavenger" pathway contributes through different mechanisms to atherosclerosis development [21]. This helps understand the aggravating effect of such oxidising substances in blood as free radicals or the protecting role of direct or indirect antioxidants such as vit. C, vit. E, Se... [22].

Table 2. Atherosclerosis and risk factors due to lipoproteinemic anomaly.

	Risk increasing factors	Risk decreasing factors
Cholesterol	Total Cholesterol ↗	Total Cholesterol ↘
	LDL Cholesterol ↗	LDLC ↘
	VLDL Cholesterol ↗	VLDLC ↘
Lipoproteins	LDL ↗	LDL ↘
	VLDL ↗	VLDL ↘
	HDL ↘	HDL ↗
Apoproteins	Apo B100 ↗	Apo B100 ↘
	Apo A1 ↘	Apo A1 ↗
	Lp B ↗	LpA1 ↗
Lipid particles	Lp (a+) ↗	
	ox LDL ↗	
	Glyc LDL ↗	
	MDA LDL ↗	
other factors	free radicals, etc..	Vit C, Vit E, Selenium, etc...

Pathogenesis of atherosclerosis

Taking into account the different theories and hypotheses on lipid infiltration, endothelial injury, and platelet role, we can state that: atherosclerosis is characterized by increased endothelial permeability, monocyte infiltration, internal smooth muscle cell (SMC) proliferation, platelet aggregation and accumulation of lipids, Ca⁺⁺ and extra cellular

matrix components such as collagen, elastin and proteoglycans in vessel wall.

Endothelial cell injury (Fig. 2)

Factors and forces promoting such damage are quite undefined and may be of physical, metabolic, hormonal, cellular, molecular or genetic nature. Among identified factors we can list: high blood pressure, anoxia, immune activation, turbulent blood factors, increases in oxidized LDL, Lp(a) or free radicals... etc. Response from irritated endothelial cells induces an increase in permeability for plasma compounds into the subendothelial space.

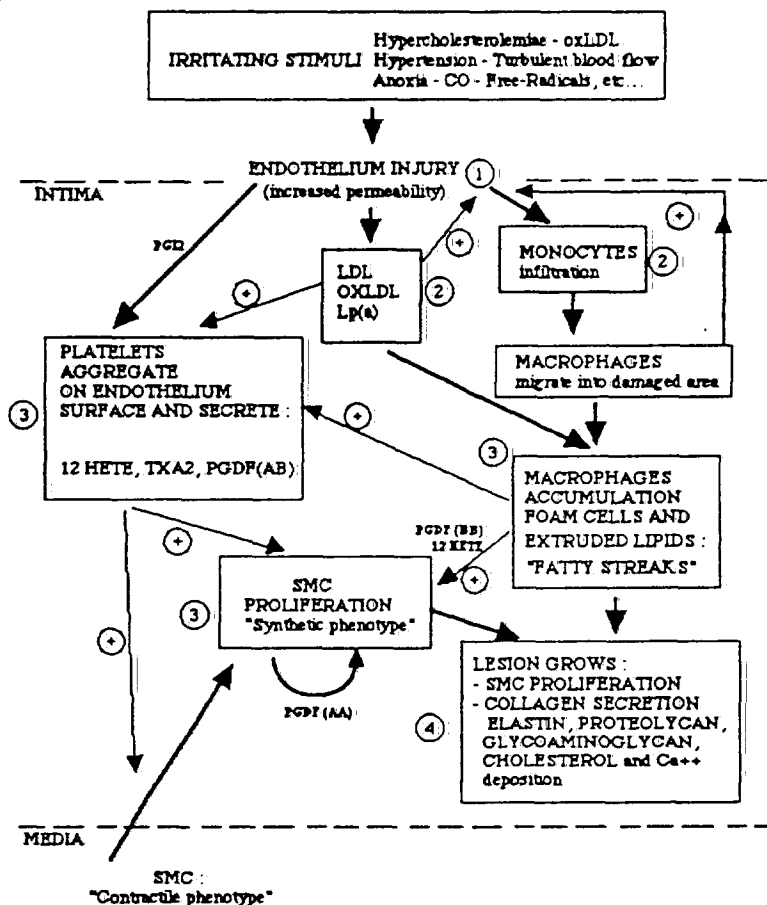


Figure 2. Pathogenesis of atherosclerosis.

Infiltration of plasma components (Fig. 2)

Endothelial injury enhances infiltration of monocytes which differentiate into macrophages, LDL and possibly Lp(a) which are oxidized by damaged endothelial cells [27]. Macrophages and oxidized LDL are chemostatic for monocytes which further penetrate into subendothelial space [22].

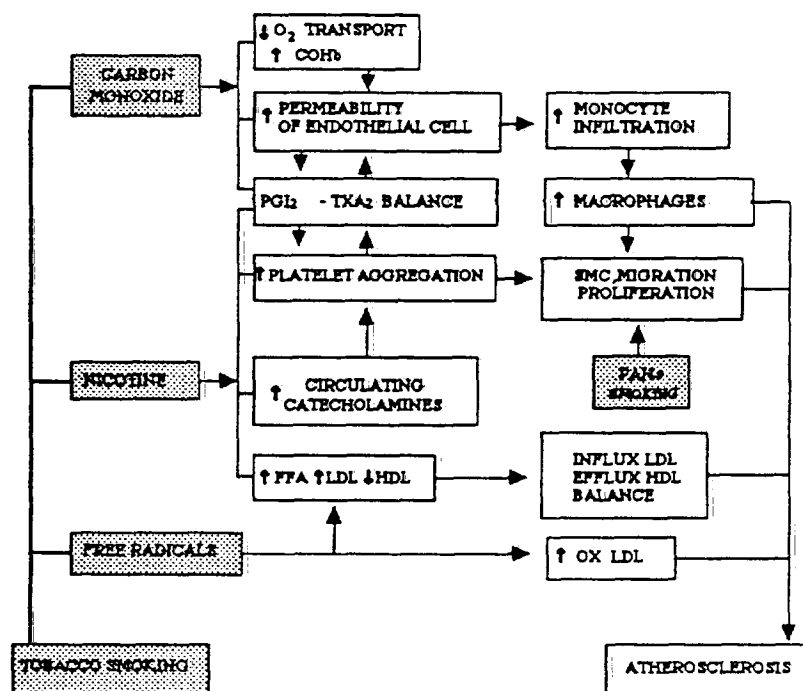


Figure 3. Smoking, CO, Nicotine, free radicals, PAHs and atherosclerosis.

Foam cell accumulation and platelet aggregation (Fig. 2)

The modified LDLs are taken up via the scavenger receptor pathway by macrophages which turn into foam cells [21,23]. Continued accumulation of macrophages in the presence of high cholesterol leads to extrusion of lipids into the arterial wall interstitial space and formation of the "fatty streak" which has become one of the pathological hallmarks of the atherosclerotic process.

Several more or less known factors cause platelets to adhere to the injured endothelium. Macrophages and platelets release growth factors

PGDF(AB) from platelets and PGDF(BB) from macrophages (Heldin) [25] which are chemostatic and mitogenic for vascular smooth muscle cells. Vascular SMC are assumed to migrate from the media to the intima where they convert from a contractile into a synthetic phenotype, proliferate and secrete growth factors (PGDFAA) [26]. At this stage, we must stress the importance of the balance between prostacycline (PGI₂) secreted by injured endothelial cells which inhibits platelet aggregation and thromboxane (TXA₂) secreted by the platelets which stimulates aggregation [27].

Progression of atherosclerosis (Fig. 2)

The hallmark in the progression of atherosclerosis is the proliferation of SMC and accumulation of extra cellular matrix in the intimal layer: collagen, elastin, proteoglycans (PGs), glycoaminoglycans (GAGs). These molecules combine with LDL, modified LDL, Lp(a), cell debris, Ca⁺⁺ deposits to form an atheroma gradually weakening and narrowing the artery, encouraging the formation of a thrombus which may develop into myocardial infarction.

Finally, there is normally a balance between cholesterol influx (LDL, Lp(a)) into the membrane and cholesterol efflux (HDL₂) out of the plasma membrane. When influx of cholesterol exceeds efflux, cholesterylesters are stored by the cells. On the other hand, the lesion progression is also dependent on SMC proliferation and consequently on the balance between growth promoters (PGDF, TXA₂, 12 HETE) and growth inhibitors (PGI₂).

This is just an overview of atherosclerosis pathogenesis which does not cover the abundant literature documenting such factors as :

- Lipoperoxydation of polyunsaturated fatty acids leading to MDA-LDL [18],
- Free radicals and antioxidising role of plasma [28] selenium,
- The role of Ca⁺⁺ as a second messenger involved in regulating processes in the vessel wall [27] promoting LDL receptor binding, inducing monocyte and SMC chemotaxis and stimulating secretion of collagen and other components.

ATHEROSCLEROSIS AND CIGARETTE SMOKING

A number of epidemiologic studies have brought evidence of association between active smoking and atherosclerosis development but the physio-biochemical mechanisms suggested are not yet definite as many smoke constituents are likely to be involved.

Mainstream smoke chemical composition

About 4,000 components have been identified in mainstream smoke. In the gas phase the major constituents are: carbon dioxide, carbon monoxide,

nitrogen oxides, nitrosocompounds, hydrogen cyanide, formaldehyde, acrolein and benzene. The biologically active compounds, however, are found in the particulate phase: nicotine, phenol, benzo(a)pyrene, nitrosamines, pyrene, naphthalene, etc...

A number of investigations of smoke toxicity have been carried out in using all mainstream smoke or tars, which cannot lead to incriminate any specific chemical substance. The primary stimuli involved in atherosclerosis development are nicotine, carbon monoxide (CO) [54], while PAH and free radicals have also been investigated.

Mainstream smoke (MS) stimuli (Fig. 3)

1. Nicotine alone or in conjunction with cigarette smoking is known to increase sympathetic nervous activity and release catecholamines from adrenal glands or cardiac tissues [52].
2. Increase in blood pressure and heart rate: this effect can be readily explained by direct action of nicotine or by catecholamine action on myocardial contractile function [30].
3. Effects on lipids: Increase in free fatty acids (FFA): intravenously injected nicotine raises plasma concentration of FFA through enhanced lipolysis. FFA mobilisation from adipose tissue is a consequence of sympathoadrenal stimulation [31] but increases the delivery of FFA to the heart and therefore increases oxygen consumption [32].

Lipoproteins: a number of studies have shown that in smokers' plasma HDL tend to be lower and LDL slightly elevated. The most important aspect could be the sharp decrease in the anti-atherogenic HDL2 cholesterol fraction [33]. The data on association between CHD and HDL subfraction is controversial and recent studies [34] find no statistically significant HDL decrease associated with cigarette smoking. Alcohol consumption, however, correlates positively with HDL cholesterol subfraction. Finally, the effect of smoking on HDL cholesterol does not seem to be cumulative and can be reversed in just 30 days after cessation of smoking (Moffsat R.) [33].

4. Platelets: Cigarette smoking induces a marked, transient increase in platelet aggregability [35, 36]. The responsible agent is likely to be nicotine which can produce the same effect in vitro. On the other hand, cigarette smoking induces increased PAF-LL (Platelet-Activating-Factor-Like-Lipid(s)) which cause LDL oxidation and then pathogenesis of smoking-induced atherosclerosis [37].

5. PGI₂-TXA₂ Balance: Cigarette-smoking affects the balance of vascular prostanoid synthesis PGI₂-TXA₂ by decreasing PGI₂ synthesis by vascular endothelial cells [38], increasing release of TXA₂ platelets [40] and incidentally platelet aggregation and SMC constriction. In fact, the direct role of nicotine and its action as a function of dose and in presence of CO is still controversial [41].

6. Carbon monoxide: Carbon monoxide forms carboxyhaemoglobin, reduces blood oxygen-carrying capacity and causes hypoxemia. Mean COHb

levels in smokers are about 5 % but may reach 10 % and more in heavy smokers. CO can affect permeability of endothelial wall, fibrinogen retention by arterial wall and PGI_2 - TXA_2 balance [41].

7. Polycyclic Aromatic Hydrocarbons (PAHs): By weekly PAH injections in pectoral muscles of white carneau pigeons, Revis [42] showed that PAH such as Benzo(a) pyrene (BaP) with the exclusion of BeP, might be the only potential atherogen in avian atherosclerosis. Randerath [43] also demonstrated on mice dermally treated with cigarette tar presumably containing aromatic compounds like BaP, induced lesions in heart DNA in a tissue specific manner. However, the administration route, the doses and the species, cannot convincingly lead to the conclusion that it is an atherosclerosis risk for a smoker.

8. Free radicals: We know that smoke contains free radicals and that free radicals are found in the atheroma plaque. Free radicals have been implicated in cardiac ischaemic artery [44] and congestive heart failure [45]. Free radicals can cause lipoperoxidation of unsaturated fatty acids and then form MDA (Malondialdehyde). LDL malonisation then leads to increased fixation on macrophages with foam cell production [57].

To sum up (Fig. 3), consistent evidence is now available to explain the aggravating effect of tobacco smoke on atheroma plaque. Nicotine and carbon monoxide are the identified primary stimuli causing a chain of biochemical reactions accelerating the atherosclerosis process [54]. Free radicals and polycyclic aromatic hydrocarbons are among the molecules recently incriminated but their precise role and mode of action require further investigation.

ATHEROSCLEROSIS AND PASSIVE SMOKING

ETS exposure has no marked effects on atherosclerosis parameters. This is due to the fact that amounts of active compounds which penetrate into the body are on the whole very small even for heavy exposures, as is most convincingly demonstrated by Scherer [46] (Table 3). The findings provide experimental evidence that for passive smoking, exposure to the gas phase of ETS is more important than to the particulate phase. In contrast to smoking, uptake of tobacco smoke derived particles during passive smoking seems to be very low and not detectable by usual methods [46]. Therefore, nicotine and cotinine in smokers reflect smoke particle exposure whereas in passive smokers these parameters indicate exposure mainly to tobacco smoke vapour phase.

Let us consider the blood stimuli generated by ETS, likely to contribute to atherosclerosis process.

Co-CoHb

As Carbon monoxide is mainly a vapour phase compound of sidestream

Table 3. Estimated dose ratio between smoking and passive smoking from G. Scherer [46].

Tobacco smoke constituents	Smoking S (20 cig/d)	Passive smoking PS (8 h/d)	Dose ratio S/PS
gaseous phase			
CO (mg)	40-400	14.4-96	2.7-4.2
Volatile nitrosamines (ug)	0.05-1.0	0.03-0.4	1.5-2.6
Benzene (ug)	200-1200	40-400	3-5
Particulate matter			
Particles (mg)	75-300	0.024-0.24	1250-3000
Nicotine (mg)	7.5-30	0.08-0.4	75-90
Benzo(a)-pyrene (ug)	0.15-0.75	0.001-0.011	75-150
Tobaccospecific nitrosamines (ug)	4.5-45	0.002-0.010	2300-4500

smoke, an exposed non-smoker shows a significant increase in CoHb after heavy ETS exposure. However, CO uptake is 2.7 to 4.2 times lower than in an active smoker (table 3) [46]. CoHb levels obtained range from 0.5 to 1.5% (National Research Council 81, Aronow 78, Wald 81 [47], Davis [48], though Sherer [46] found a higher CoHb value 6 % after 8 hours' exposure. In fact, 1% CoHb is considered to be representative of average tobacco smoke exposures, which is not far from levels observed in exposures to other CO sources: cooking, heating, exhaust fumes, etc... (3 % CoHb in non-smoking taxi drivers in London). In active smokers, however, CoHb levels are much higher: 5% and more. Moskowitz [47] found that whole blood 2-3 diphosphoglycerate (2-3 DPG) was higher in smoke-exposed than in unexposed children, which shows that the organism attempts to compensate for hypoxia by increasing 2-3 DPG level in blood to meet tissue oxygen requirements. However, the results are significant for boys only.

Nicotine

In a non-smoker, plasma nicotine rises so faintly after exposure to tobacco smoke that variations observed are sometimes not significant. Regarding significant quantities absorbed, Sherer [46] has recently shown (table 3) that an active smoker's (S) uptake is 75 to 90 times that of a passive smoker (PS). Regarding plasma, salivary or urinary concentrations, Jarvis [49] has found that the ratio is about 100. In these circumstances, direct or indirect action of nicotine on an ETS exposed non smoker can only be very weak.

Lipids

Only a few studies have investigated this aspect. Moskowitz [47] found that High Density Lipoprotein (HDL) cholesterol was lower in ETS exposed children; the HDL2 cholesterol subfraction was decreased but in boys only.

while the HDL3 cholesterol subfraction, was decreased in girls only and curiously, together with Low Density Lipoprotein (LDL) cholesterol subfraction. These results are not consistent enough to permit a definite conclusion inasmuch as other parameters ApoA1, ApoB or better LpA1, LpB are now considered to be better correlated with atherosclerosis risk. Further research work is necessary to evaluate effects of ETS on lipidic fractions, all the more so as in active smokers, variations of HDL subfractions are not very significant either [34].

Platelets

Passive smoking increases platelet aggregation and produces a desquamation effect on endothelial cells of a similar magnitude to that observed in active smoking [48]. Davis [48] thinks that even a small increase in plasma nicotine concentration may release catecholamines.

Polycyclic Aromatic Hydrocarbons (PAHs)

Although PAHs are potentially very harmful because of their carcinogenic effect on the lungs, bladder and heart through formation of adducts, it is questionable whether they are actually playing a role in the case of ETS. Indeed, the amounts thus absorbed are so small compared on the hand to those of an active smoker who inhales from 75 to 150 times more, according to Scherer [46] (table 3) and on the other hand to amounts contributed by the environment (50) as in the case of benzene which brings about ten times more. Grimmer [50] has demonstrated that sidestream smoke (SS) contains ten times more PAHs (Benzo(a)pyrene for instance) than mainstream smoke (MS). 99 % of these PAHs, however, occur in the particulate phase whereas a non-smoker is only exposed to the vapour phase [46].

When recapitulating available evidence on ETS generated stimuli in the body, it appears that increases in nicotine and CoHb levels are so low that only very low variations can be expected from direct actions or catecholamine releasing mechanisms. Effects on lipids are just about significant. Effects on platelet aggregation seem to be a more promising avenue of research as platelets influence both the slowly developing atherosclerosis process and more important still, the rapidly developing phase of thrombus formation preceding a cardiac incident.

CONCLUSIONS

About 10 epidemiologic studies conducted in different countries have concluded that ETS exposure accounts for about 30% risk increase of CHD mortality. Because of the many factors, some of which have only been recently discovered, that play a role in the development of CHD, a number of these studies have not been properly designed even if some (Svendsen, Garland, He-Hole) have controlled for age, race, weight, hypertension, alcohol consumption, exercise and total serum cholesterol. Many other

factors need to be considered: diabetes, heredity or associated lipidic factors, Apo A1, Apo B, Lp A1, Lp(a), platelet factors, diet (antioxidizing factors, vit E, vit C, selenium) etc... In addition to those, should of course be listed all the confounding factors currently found in ETS epidemiologic studies and generally connected with exposure assessment (intensity, duration).

As in the case of lung cancer, it is now certain that active smoking increases the risk of fatal CHD: the risk is supposed to be about 2.0 (Framingham) but may vary from 1.6 to 2.0 for a cigarette smoker but from 1.08 to 1.40 only for a pipe smoker (Surgeon General Report) [54]. Some of the most important action mechanisms of mainstream smoke by means of nicotine, CO (CoHb), platelet aggregation are now fairly well known. However, its action on coronary atherosclerosis remains unexplained as available evidence is inconsistent and even contradictory. The fact that CHD risk decreases rapidly after cessation or diminution of smoking [51] may indicate that effects of smoking are more severe on thrombosis [52] or infarction than on coronary atherosclerosis. As far as ETS action is concerned, increases in plasma nicotine and CoHb levels are extremely low compared to those in active smoking (1 % for the former, 20 % for the latter). The physiobiochemical effects actually observed on an exposed non-smoker are real: HDL and HDL2 are decreased and platelet aggregation increased, they indicate that the role of ETS in CHD incidence is biologically plausible.

It is, however, unrealistic, given our present knowledge, to suggest new mechanisms, inspired for instance by animal experimentation and which would not first apply to active smoking. Indeed, an active smoker is also a passive smoker who inhales his own smoke as well as that of others. Therefore, the magnitude of risk in an ETS exposed non-smoker is bound to be very small compared to that of an active smoker. This risk has certainly been overestimated in some studies: a scientist's common sense is baffled when relative risk estimates of ETS exposure are equal or even higher than those of active smoking (Garland, Gillis, Svensen, Hole). Is a smoker more intoxicated by ETS than by mainstream smoke ?

This suggests that mean RR of CHD due to ETS exposure calculated from available epidemiologic studies, has probably been overestimated as at the moment it cannot be explained by physiobiochemical changes caused by ETS in the body. Among the mechanisms suggested by Glantz, CoHb (at 1 %) and P.A.H. (PS/S = 1/100) incidence is unconvincing. However, action on platelet aggregation is more likely. Reversibility of action suggests that incidence is stronger on thrombosis process than on coronary atherosclerosis development. Therefore, Well's [11] extrapolation to the North American population leading to a very high CHD mortality due to ETS appears to be questionable even though he maintains it against critiques [55].

A number of very carefully conducted studies will be necessary before correct risk assessment and satisfactory physiobiochemical interpretation can be achieved.

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Carbon Monoxide and Cardiovascular Disease: An Analysis of the Weight of Evidence

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The role, if any, of environmental tobacco smoke (ETS) in the causation and/or exacerbation of cardiovascular disease remains to be proven and defined. Earlier workers suggested that ETS-associated carbon monoxide, nicotine, and/or polycyclic aromatic hydrocarbons may be causative factors. The purpose of this review was to assess the weight of evidence supporting a role for ambient carbon monoxide in the etiology of human ischemic cardiovascular disease. The findings show that there is scant clinical or experimental evidence to support a role for carbon monoxide in the causation of ischemic heart disease. Further, the results of field studies of relative air quality in nonsmoking and smoking homes, offices, and public places show that ETS contributes only minor and toxicologically insignificant increments in ambient carbon monoxide concentrations. These increments are variable and easily masked by other common carbon monoxide sources such as internal combustion engines and the burning of cooking and heating fuels. It is concluded that if ETS plays a role in the etiology of cardiovascular disease, it is most likely not mediated through carbon monoxide. © 1993 Academic Press, Inc.

INTRODUCTION

Cigarette smoking is frequently implicated as a risk factor in the production and/or exacerbation of cardiovascular disease. Active smoking has been estimated to impart a risk for heart disease of 1.7 relative to nonsmoking (Surgeon General, 1983).

Since 1984 a number of epidemiological studies have been conducted to assess the presence or absence of an association between the cohabitation of nonsmokers with smokers and death from cardiovascular disease. Glantz and Parmley (1991) reviewed the results of 13 such studies and pointed out that in most (9/13, 69%) the estimated relative risk (RR) of cardiovascular death due to ETS exposure was not significantly different from that of non-ETS-exposed people. In the remaining 4 studies (31% of the studies reviewed) small elevations in RR, ranging from 1.2 to 2.0, were considered statistically significant.

Glantz and Parmley noted that although estimates of cardiovascular death risks were only inconsistently elevated in ETS-exposed subjects, risk was not randomly distributed around unity. The computed RRs and 95% confidence intervals (CI) appear to be skewed toward elevation. Further, when the results from all studies were pooled,

analysis revealed a statistically significant 30% increase in risk ($RR = 1.3$; 95% $CI = 1.2$ to 1.4).

Reviewers of the ETS-cardiovascular death risk issue (Glantz and Parmley, 1991; NIOSH, 1991; Taylor *et al.*, 1992; and Steenland, 1992) all noted that the known cardiotoxic compounds identified in mainstream smoke are also present in ETS. This has been considered supportive evidence for the thesis of a cause-and-effect relationship between ETS and cardiovascular disease risk. But in reaching their conclusions it is obvious that those authors gave little or no thought to one of the most basic principles of toxicology—the concept of dose-response relationships.

It is a basic tenet of both clinical and experimental toxicology that there is generally a direct relationship between the amount of chemical to which an organism is exposed and the magnitude of the physiological changes produced. This principle of dose-response relationships forms the basis through which the medical profession, industrial hygienists, and federal regulators establish nontoxic doses of drugs, acceptable daily exposure levels to food additives, and no effect levels of chemicals in the environment. Disregarding the principle of dose-response relationships would necessarily obligate prohibition of human exposure to virtually all chemicals, whether synthetic or natural.

Because of the relationship between dose and effect, the detection of a substance in the environment is only the initial step in establishing the presence of a possible human health hazard. When appraising the human health implications of exposure to any environmental factor a thorough assessment of the biological and chemical plausibilities of the purported effect is imperative. Such an assessment should address three key factors: (1) Is there a plausible toxicologic mechanism through which the material could produce the suspected effect? (2) Is the mechanism operative in the human subjects of interest? (3) Are the human subjects exposed to a sufficient quantity of the environmental factor to produce the claimed toxicological consequence?

The mechanism(s) through which either active or passive smoking might increase risk of cardiovascular disease have yet to be unequivocally defined. A prominent and frequently mentioned cause or contributor is the production of myocardial ischemia through exposure to ETS-associated carbon monoxide (Glantz and Parmley, 1991; NIOSH, 1991; Taylor *et al.*, 1992; and Steenland, 1992). The purpose of this review is to weigh the evidence relative to the hypothesis that ETS-related exposures to carbon monoxide (CO) can contribute to either the initiation or exacerbation of ischemic cardiovascular disease in humans. The results of this review show that there is little clinical or experimental evidence that is relevant to the issue and that that which is available does not support a role for ETS-associated carbon monoxide in the causation or exacerbation of ischemic heart disease in non/never-smoking humans.

MECHANISM OF ACTION OF CARBON MONOXIDE

Carbon monoxide, produced during the incomplete combustion of all organic materials, is the most extensively studied and best understood component of either mainstream or sidestream cigarette smoke. This gas avidly competes with oxygen for binding to hemoglobin (Hb). The combination of CO with Hb results in the formation of carboxyhemoglobin (COHB) and compromises the transport of oxygen to the tissues of the body.

All consequences of exposure to CO are directly attributable to the production of tissue anoxia. The magnitude of anoxia, and therefore the severity of physical symp-

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toms, is related to the percentage of hemoglobin that is converted to COHb. The production of COHb is proportional to the amount of CO present in the inspired air.

The remarkable affinity of hemoglobin for the CO molecule makes the gas deceptively toxic. If the affinity of hemoglobin for oxygen is assigned a value of 1.0, its affinity for CO is greater than 200. In the clinical situation, a few minutes of inhaling air containing as little as 0.1% CO (i.e., 1000 parts per million) results in 50% of the available hemoglobin being converted to COHb. The presence of a 50% saturation of COHb is physically incapacitating and may even be lethal to the human (Smith, 1986). Toxicological consequences such as headache, dyspnea, and visual disturbances are associated with lower blood concentrations of COHb and the American Conference of Governmental and Industrial Hygienists has indicated its intent to establish 3.5% COHb as its best estimate of a no effect concentration among industrial workers chronically exposed to CO (ACGIH, 1991).

Because of the critical importance of continuous and adequate oxygenation of heart muscle, it is obvious that a cardiotoxic effect of CO is plausible. Myocardial damage caused CO-induced ischemia would be no less significant than ischemic damage secondary to coronary thrombosis or atherosclerosis. Since tobacco smoking may increase the concentration of CO in certain environments it is reasonable to assess the sensitivity of humans to CO-induced cardiotoxicity and determine the quantitative impact of indoor smoking on the CO concentration in air.

CARDIOVASCULAR EFFECTS OF CARBON MONOXIDE IN HUMANS

Stern *et al.* (1988) presented evidence of a possible CO-induced risk of cardiovascular disease in humans exposed to automobile exhaust. These workers reported a 35% excess in ischemic heart disease deaths among male traffic officers employed in tunnels in New York City. Additional evidence of probable occupational association of the deaths was the fact that elevated risk promptly declined upon cessation of the occupational exposure.

These officers were occupationally exposed to environments containing about 50 ppm of CO. Although direct measures of COHb were not reported, it has been estimated that 8 hr of exposure to 50 ppm of CO will produce a COHb concentration of 6.27% (Singh *et al.*, 1991). This indicates that the traffic officers may have had blood concentrations of COHb approximately twofold greater than the ACGIH no effect concentration.

Several investigators have studied the effects of controlled tobacco smoke or CO inhalation on exercise tolerance and cardiac rhythms. Elevated serum carboxyhemoglobin levels have been associated with decreased exercise tolerance in healthy subjects (McMurray *et al.*, 1985) and decreased exercise tolerance and increased susceptibility to exercise-induced cardiac arrhythmias in patients with coronary artery disease (Allred *et al.*, 1989; Sheps *et al.*, 1990a,b). Other workers, however, have reported the absence of effects of exposure to low concentrations of CO in patients with known coronary artery disease (Hinderliter *et al.*, 1989).

Effects in healthy human. McMurray *et al.* (1985) exposed healthy smokers and nonsmokers to cigarette smoke during strenuous exercise. These workers reported that the exposure decreased the amount of exercise required to produce exhaustion in both groups. In addition, exercise-associated changes in biochemical measurements indicated that exposure to smoke caused an increased reliance on anaerobic metabolism, evidence

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of decreased tissue oxygenation. The authors attributed these changes to systemic anoxia secondary to the formation of COHb.

McMurray *et al.* stated a belief that the exposure of their subjects was similar to a typical exposure of humans to environmental tobacco smoke. They did not, however, present quantitative information to support this contention and it is possible that their subjects were exposed to unrealistically high levels of smoke.

During the exercise portions of the experiment cigarettes were mechanically smoked, at a rate of one every 3 min, and the smoke was mixed with air and delivered directly to exercising subjects via a mouthpiece and an inhalation tube. The minimum duration of exercise was 20 min. Consequently, subjects were exposed to the smoke from approximately seven cigarettes during their exercise session. Preexercise COHb concentration in nonsmoking subjects was 1.1% and at the conclusion of the experimental session it had risen to 2.2%. Similar data for subjects who were smokers was not presented.

While the smoke exposure regimen in the McMurray *et al.* study may have caused the slight decrement in exercise performance, the relevance of the data to the exposure of humans to ETS is difficult to assess because the authors failed to report either the smoke:air ratios in the mixtures delivered to their subjects or the CO concentrations to which they were exposed. Since subjects were exposed to some portion of the smoke from approximately seven cigarettes it is possible that unrealistically high ETS and CO concentrations were used.

Levesque *et al.* (1991) studied the relationship between CO in ambient air and the formation of COHb in hockey players under game conditions. These workers found that for every 10 ppm of CO in environmental air, COHb saturation increases by 0.76%. If a similar relationship holds for McMurray's exercising subjects it is estimated that the nonsmoker's experimental exposure was to 15 ppm of CO in excess of their normal background concentrations.

Effects in humans with coronary artery disease. Studies in which coronary-artery-diseased subjects were exposed to CO prior to exercise have yielded a variety of results. These variable results are doubtless due to differences in experimental designs and measured endpoints and subject selections.

Kleinman *et al.* (1989) reported that exposure of male subjects with stable angina to 100 ppm of CO for 1 hr increased COHb saturation from a preexposure 1.5% to 2.9%. The 2.9% COHb concentration caused a more rapid onset of exercise-induced anginal pain than was experienced during the control exercise period without CO exposure.

Hinderliter *et al.* (1989) exposed coronary-artery-diseased patients, with low baseline levels of ventricular arrhythmias, to either 100 or 200 ppm of CO for sufficient durations to increase COHb levels to as high as 5.8%. Subjects then performed symptom-limited exercise. Continuous ambulatory EKG monitoring revealed that this level of COHb saturation was nonarrhythmogenic in these cardiac-diseased patients. Unfortunately, these workers did not compare pre- and postexposure susceptibility to anginal pain.

Using the same protocol with coronary-artery-diseased patients who had ventricular arrhythmias Sheps *et al.* (1990a,b) found that 5.7% COHb saturation caused an increased frequency and complexity of postexercise ventricular arrhythmias. Carboxy-hemoglobin saturation of 3.9%, however, was without effect.

Allred *et al.* (1989) reported the results of a multicenter study of the effects of CO exposure on exercise performance in coronary artery disease patients. Subjects were

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exposed to either 117 or 253 ppm of CO for periods sufficient to elevate COHb concentrations to values of 2.0 or 3.9%. Under the conditions of these experiments control COHb concentrations were unusually low (0.6–0.7%). These workers reported that both the 2.0 and the 3.9% COHb concentrations exacerbated exercise-induced myocardial ischemia as evidenced by EKG changes and decreased time of onset of anginal pain.

The Allred study has been criticized (Katzenstein, 1990) because of the low control values reported for pretest blood COHb concentrations. Levels of COHb in nonexposed nonsmokers are generally found to be from two to three times higher than those reported by the Allred group. For example, Hinderliter *et al.* (1989) reported a preexposure level of 1.8%; Sheps *et al.* (1990a) reported 1.82%; and McMurray *et al.* (1985) reported 1.1%.

The Allred group explained that their low levels were due to their use of a gas chromatography assay of COHb rather than the more frequently used optically based assay (Dahms *et al.*, 1990). They stated that the commercial instruments generally provide inaccurately high COHb readings when concentrations of less than 5% are assayed. For this reason the relevance of the Allred data to other contemporary studies is open to question.

Overall, the results of studies in humans afford some evidence that exposure to extremely high concentrations of CO may elevate risk of ischemic heart disease and decrease the exercise tolerance of people with coronary artery disease. Such effects are consistent with the production of systemic anoxia and impaired myocardial oxygenation. However, it remains to be established whether ETS can contribute sufficient environmental CO to impact on the cardiovascular status of either healthy or compromised humans.

THE CLINICAL SIGNIFICANCE OF ETS-ASSOCIATED CARBON MONOXIDE

To assess the potential cardiac risk of exposure to ETS-associated CO, it is necessary to estimate a maximal COHb saturation that would produce no physiological changes in exposed humans. Concentrations of CO in excess of that value should be considered potentially dangerous to human health.

A COHb concentration of 2.5% is proposed as the no effect level. This level of saturation is far below that which was associated with increased ischemic heart disease risk in traffic tunnel workers (estimated to be 6.27% COHb) (Stern *et al.*, 1988). It is also well below the 3.9% level, a level that did not result in exercise-induced arrhythmias in patients with preexisting coronary artery disease (Sheps *et al.*, 1990a,b) and it is less than the 2.9% level that was associated with decreased exercise tolerance in coronary-artery-diseased patients (Kleinman *et al.*, 1989).

The proposed value is also lower than the 3.5% COHb saturation that the ACGIH intends to establish as its best estimate of a no effect concentration among industrial workers (ACGIH, 1991). The ACGIH value represents that body of health scientists' best estimate of a chronic, no effect level in workers exposed to CO 8 hr per day, 40 hr per week.

The 2.2% COHb concentration reported by McMurray *et al.* (1985) to produce an 8% decrement in the performance of strenuous exercise was not considered because

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the effect, which was minimal, was noted in only a small number of strenuously exercising subjects. Similarly, the 2.0% COHb saturation reported to reduce exercise tolerance in patients with coronary artery disease (Allred *et al.*, 1989) was not incorporated into the estimation of a no effect level because of uncertainty about the comparability of the COHb analyses in that study with those of the more numerous contemporary studies. In view of the available data relative to potential cardiovascular effects of CO exposure in humans, the 2.5% COHb concentration represents a conservative estimate of a probable no effect level.

The likelihood of a human achieving a serum concentration of 2.5% COHb depends upon the ambient concentration of CO and the duration of exposure. Singh *et al.* (1991) reviewed experimentally achieved COHb concentrations after exposures of varying durations to different concentrations of the gas. With exposure to 100 ppm, a serum concentration of 2.5% COHb was reached after between 30 and 45 min of exposure. At an ambient concentration of 50 ppm CO, longer than 60 min was required; and two hours exposure to 45 ppm causes a COHb concentration of 2.48%.

With the exception of accidents, employment in occupations involving internal combustion engines, and intentional self inflicted exposures, humans are seldom exposed, even for brief periods, to CO concentrations in the range of 45 to 100 ppm. At lower, more probable levels of CO exposure still longer periods are required to produce the 2.5% COHb saturation. For example, exposure to 15 ppm of CO requires continuous exposure for 10 hr to produce a serum concentration of 2.5% COHb (Guerin *et al.*, 1992).

IMPACT OF ETS ON AMBIENT CARBON MONOXIDE CONCENTRATIONS

It has been frequently and correctly noted that sidestream tobacco smoke contains a higher concentration of CO than does mainstream smoke. Sidestream smoke is produced at a lower temperature at which the combustion of carbonaceous materials is less complete. American cigarettes are recognized to deliver approximately 15 mg/cigarette of CO via mainstream smoke and 50 mg/cigarette via sidestream smoke (Guerin *et al.*, 1992).

This relatively high concentration in sidestream smoke has led many to conclude that ETS is a major contributor to environmental CO concentrations. Such a conclusion is not supported by the results generated in field studies during which the air in residences, work places, and public places has been analyzed under both smoking and nonsmoking conditions.

Guerin *et al.* (1992) reviewed the data generated during field studies of CO concentrations in a variety of smoking and nonsmoking areas. The results of the reviewed studies indicated that in general, smoking contributes only small increments in environmental CO. For example, mean concentrations of CO in the air of offices in which smoking was permitted ranged from 1.2 to 2.8 ppm, whereas values in nonsmoking areas ranged from 1.2 to 2.5 ppm. In restaurants and cafeterias permitting smoking, the environmental CO concentrations ranged from 1.2 to 9.9 ppm as contrasted against nonsmoking control areas where concentrations ranged from 0.5 to 7.1 ppm.

On the basis of the available data obtained from field studies, it is clear that ETS contributes CO to the environment. However, the increment of environmental CO

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attributable to tobacco smoking is exceedingly small. Further, this small increase is easily masked by normal day-to-day variations in ambient concentrations which are attributable to the presence of other CO sources such as automobiles and the combustion of heating and cooking fuels.

More importantly, however, the results of the field studies also show that whether or not tobacco smoking is permitted, CO concentrations to which humans are exposed seldom exceed the 9 ppm indoor standard that has been recommended by the American Society for Heating, Refrigerating, and Air Conditioning Engineers (ASHRAE, 1989).

Since 10 hr of exposure to 15 ppm of CO is required to produce a 2.5% level of COHb saturation in humans, and since this is a no effect level, few Americans are ever exposed, even for brief periods, to cardiotoxic concentrations of COHb. The small increment in ambient CO concentrations contributed by ETS is insignificant.

While conducting this analysis no attempt was made to directly address the issue of whether or not exposure to ETS per se causes or exacerbates cardiovascular disease. The results of this review have established, however, that if the purported impact of ETS on cardiovascular disease is real, it can be neither explained nor mediated through ETS-associated increases in ambient concentrations of carbon monoxide. There is scant evidence to support a role for carbon monoxide in the causation of ischemic heart disease. Further, the results of field studies of air quality in nonsmoking and smoking homes, offices, and public places demonstrate that ETS contributes only minor and toxicologically insignificant increments in ambient carbon monoxide concentrations. These increments are variable and easily masked by other commonly encountered carbon monoxide sources such as internal combustion engines and the burning of cooking and heating fuels.

Earlier workers have suggested that inhalation exposure to environmental tobacco smoke-associated nicotine and/or polycyclic aromatic hydrocarbons may also cause cardiovascular disease in humans (Glantz *et al.*, 1991; NIOSH, 1991; Taylor *et al.*, 1992; and Steenland, 1992). Such claims cannot be taken seriously at this time since critical reviews of the experimental and clinical evidence claimed to support the hypotheses have yet to be conducted.

CONCLUSION

If ETS is an etiological factor in cardiovascular disease, its effect is most likely not mediated through carbon monoxide.

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Appendix D

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McMurray, R.G., Hicks, L.L. and Thompson, D.L., "The Effects of Passive Inhalation of Cigarette Smoke on Exercise Performance," European Journal of Applied Physiology 54(2): 196-200, 1985.

Eight women (four smokers/four nonsmokers) inhaled, through a mouthpiece, either room air or air mixed with cigarette smoke. Exercise performance was then tested on a treadmill, and blood was obtained for chemical analysis.

Smoke inhalation was reported to have a variety of adverse effects. These included: a reduction in maximal oxygen uptake during performance testing; an increase in maximal blood lactate; an increase in ratings of perceived exertion. The authors concluded that inhalation of sidestream smoke "adversely affects exercise performance." (p. 196) They stressed the possible role of elevated carboxyhemoglobin (COHB) in the reduction of exercise performance and suggested that a reported increase in heart rate during the smoke exposure reflected "an attempt to improve cellular oxygenation." (p. 199) The elevated lactate concentrations were suggested as indicating "a greater reliance on anaerobic metabolism." (p. 199)

Comment

This is a weak study, involving only eight subjects and only females. Furthermore, they were all aerobics class participants, which raises additional questions about the representativeness of the sample. Also, the study was done in a

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laboratory situation uncharacteristic of ETS exposure in the normal environment. In particular, the method of inhalation of smoke (through a mouthpiece) would be more analogous to "active" smoking than normal exposure to ETS. (Albeit, the authors argue that the relatively low levels of COHB of their subjects was typical of what might be expected from ETS exposure.)

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The effects of passive inhalation of cigarette smoke on exercise performance

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Summary. The purpose of this investigation was to evaluate the effect of passive smoke inhalation on submaximal and maximal exercise performance. Eight female subjects ran on a motor driven treadmill for 20 min at 70% $\dot{V}_{O_{2max}}$ followed by an incremental change in grade until maximal work capacity was obtained. Each subject completed the exercise trial with and without the presence of residual cigarette smoke. Compared to the smokeless trials, the passive inhalation of smoke significantly reduced maximal oxygen uptake by $0.25 \text{ l} \cdot \text{min}^{-1}$ and time to exhaustion by 2.1 min. The presence of sidestream smoke also elevated maximal R value (1.01 vs 0.93), maximal blood lactate (6.8 vs 5.5 mM), and ratings of perceived exertion (17.4 vs 16.5 units). Passive inhalation of smoke during submaximal exercise significantly elevated the CO_2 output (1.68 vs $1.58 \text{ l} \cdot \text{min}^{-1}$), R values (0.91 vs 0.86), heart rate (178 vs 172 $\text{bts} \cdot \text{min}^{-1}$) and rating of perceived exertion (13.8 vs 11.8 units). These findings suggest that passive inhalation of sidestream smoke adversely affects exercise performance.

Key words: Residual cigarette smoke — Maximal oxygen uptake — Lactate — Rating of perceived exertion — Carboxyhemoglobin

Introduction

Recently, studies have been conducted which show that non-smokers who inhale the smoke of nearby smokers are exposed to smoke constituents at levels as high as smokers who are inhal-

ing. Russell (1973) and Olshansky (1982) determined that during rest, passive inhalation of tobacco smoke increased expired carbon dioxide and blood carboxyhemoglobin levels in both smokers and non-smokers. White (1978) noted that the presence of smoke in the air caused increased resting ventilation, oxygen uptake, carbon dioxide production, heart rate and blood pressure. All of these investigations determined that passive inhalation of cigarette smoke for an extended period of time causes harmful health related problems in non-smokers (Bonham and Wilson 1981; Hirayama 1981). With these effects existing at rest, one must question what physiological effects passive inhalation of cigarette smoke would have on an exercising individual. Therefore, this investigation was designed to evaluate the effect of the passive inhalation of residual, or sidestream, cigarette smoke on submaximal and maximal exercise.

Methods

Eight moderately active, normal women taking part in an aerobics class were the subjects. They averaged 21.8 ± 2.4 years of age, 162.5 ± 5.1 cm in height, weighed 58.2 ± 2.3 kg, and had a $\dot{V}_{O_{2max}}$ of $2.57 \text{ l} \cdot \text{min}^{-1}$ ($44.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Four were smokers (>1 pack/week) and four were non-smokers. After obtaining written voluntary consent, each subject was screened by a medical history, resting 12-lead electrocardiogram, and a maximal oxygen uptake test ($\dot{V}_{O_{2max}}$). The results of the $\dot{V}_{O_{2max}}$ test were used to interpolate a workload resulting in 70% $\dot{V}_{O_{2max}}$ to be used for further testing.

Each subject completed to exercise trials using the same protocol: a control, in which the subject breathed no cigarette smoke and an experimental trial in which the subject breathed air mixed with cigarette smoke. The order of the trials was counter-balanced and the subjects received no information concerning whether the session was a control or experimental

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trial. Room temperature was $22.5 \pm 0.9^\circ\text{C}$ for all trials. No strenuous physical activity was allowed for 24 h preceding either trial, both took place during the pre-ovulatory phase of the subjects' menstrual cycles.

The subjects reported to the lab after abstaining from eating for four hours, and for the smokers, abstaining from smoking for the past twelve hours. Height and weight were measured. ECG leads were attached. The subject then rested quietly seated on a chair on the treadmill. After 5 min of rest the subject began breathing through a mouthpiece and valve. During the tenth minute of rest, heart rate, minute ventilation, oxygen uptake and carbon dioxide output were measured. The subject then rested for an additional 5 min during which, in the experimental trial only, smoke was injected into the inspired air. All measurements were repeated.

Once resting measurements were completed, the subject ran for 20 min at approximately 70% of their $\dot{V}_{O_{2\max}}$. Heart rate was monitored continuously and recorded for the last ten seconds of each minute. Oxygen uptake and CO_2 output were measured every fifth minute. End-tidal CO_2 and O_2 were measured for six seconds at the end of each five minute segment. During the final minute of the run a rating of perceived exertion (RPE) was obtained (Borg 1973). Then without stopping, the treadmill grade was increased by 2.5% every 2 min thereafter until the subject indicated that she could no longer continue the exercise. During the last minute of each incremental stage and the final minute of exercise \dot{V}_E , \dot{V}_{O_2} and \dot{V}_{CO_2} were measured. $P_{\text{ET}}\text{CO}_2$ and $P_{\text{ET}}\text{O}_2$ were measured for the last six seconds of each stage. Heart rates were monitored and recorded the last ten seconds of each minute. RPE was obtained at the end of exercise. Five minutes post exercise a venous blood sample was obtained from an antecubital vein for carboxyhemoglobin and lactate analysis.

Instrumentation

Oxygen uptake (\dot{V}_{O_2}) and carbon dioxide output (\dot{V}_{CO_2}) were calculated based on open-circuit spirometry. Minute ventilation was obtained from a dry gas meter adapted to drive a chart recorder. Fractions of expired O_2 and CO_2 were measured from a mixing chamber using oxygen (Applied Electrochemistry S-3A) and carbon dioxide (Beckman LB-2) analyzers. $P_{\text{ET}}\text{CO}_2$ and $P_{\text{ET}}\text{O}_2$ were measured at the level of the mouthpiece using a modified triple l-valve and previously mentioned gas analyzers adapted to the breathing valve. Venous blood was analyzed for lactate using the Strom Technique (Strom 1949). Carboxyhemoglobin levels were obtained by co-oximetry (Instrumentation Laboratory). Statistical interpretation of the data was completed using either a one-way or two-way analysis of variance with repeated measures. A Tukey HSD test was applied a posteriori when necessary to determine the exact nature of the significance. The 0.05 level of significance was used for all computations.

During the smoke trials a pump apparatus was employed that simultaneously smoked cigarettes, captured the smoke and pumped the smoke into the inspired air. The cigarettes were smoked by the machine at a rate of one per four minutes at rest and two per six minutes during exercise. The pump apparatus was positioned out of sight of the subjects. No smoking occurred before the subject had been on the mouthpiece and noseclips for at least 5 min. The pump was turned on for both trials so that the sound of the motor would be similar for both experiments. Also, the subject was given no information as to which trial involved the smoke until both trials were completed.

Results

Maximal oxygen uptake during the control trials was $2.39 \pm 0.15 \text{ l} \cdot \text{min}^{-1}$ or $41.1 \pm 2.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (Fig. 1). Passive inhalation of smoke significantly reduced the $\dot{V}_{O_{2\max}}$ to $2.13 \pm 0.14 \text{ l} \cdot \text{min}^{-1}$ or $36.6 \pm 2.6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($p < 0.05$). It also reduced the duration of exercise from $25.75 \pm 0.85 \text{ min}$ to $23.63 \pm 1.16 \text{ min}$ ($P < 0.05$). The presence of smoke increased the maximal R value from 0.93 ± 0.03 during the controls to 1.01 ± 0.04 indicating a greater CO_2 output at a given \dot{V}_{O_2} . The rating of perceived exertion at the end of the control trials averaged 16.5 ± 0.6 units and was significantly increased to 17.4 ± 0.6 units during the smoke trials (Fig. 2). Maximal heart rate responses were similar for both conditions, averaging 194 ± 2

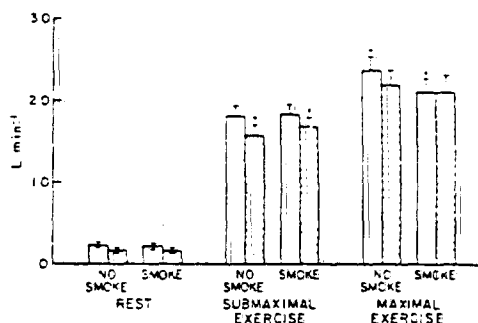


Fig. 1. Mean (\pm SEM) \dot{V}_{O_2} and \dot{V}_{CO_2} ($\text{l} \cdot \text{min}^{-1}$) at rest and during exercise with (hash marks) and without (open) smoke inhalation. * significant difference ($p < 0.05$) no smoke vs smoke

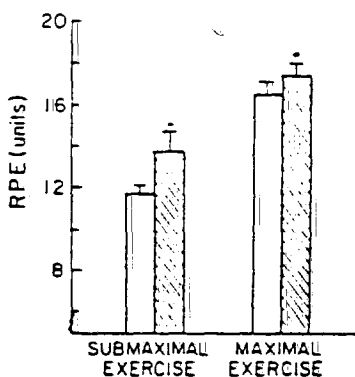


Fig. 2. Rating of perceived exertion during submaximal and maximal exercise with (hash marks) and without (open) smoke inhalation (Mean \pm SEM). * significant difference ($p < 0.05$) no smoke vs smoke

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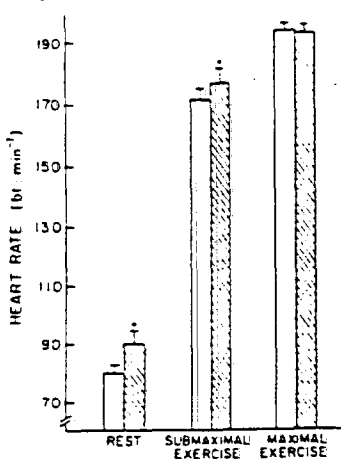


Fig. 3. Heart rate responses at rest and during exercise with (hash marks) and without (open) smoke inhalation (Mean \pm SEM). * significant difference ($p < 0.05$) no smoke vs smoke

bts \cdot min $^{-1}$ (Fig. 3). Post exercise venous blood lactates averaged 6.8 mM during the smoke trials, significantly greater than the controls (5.5 mM). As noted in Table 1, similarities between controls and smoke trials existed for maximal minute ventilation, $P_{ET}CO_2$, and P_{ETO_2} . The presence of smoke increased the \dot{V}_E/\dot{V}_{O_2} ratio at maximal exercise from a mean of 30.5 to 33.5 l of air per liter of oxygen ($P < 0.05$).

Submaximal exercise resulted in an oxygen uptake of 1.82 ± 0.09 l \cdot min $^{-1}$ (31.3 ± 1.6 ml \cdot kg $^{-1}$ \cdot min $^{-1}$) during the control trials which represented $73 \pm 3\%$ $\dot{V}_{O_{2max}}$ (Fig. 1). Inhalation of smoke did not significantly affect the submaximal \dot{V}_{O_2} (1.85 ± 0.08 l \cdot min $^{-1}$) but increased the relative intensity to $76 \pm 3\%$ of the smoking trial

$\dot{V}_{O_{2max}}$. The inhalation of smoke significantly elevated the CO_2 output by 100 ml \cdot min $^{-1}$; $P < 0.05$ (Fig. 1). Consequently, R values were also increased with passive smoking (controls = 0.86 ± 0.02 vs smoke = 0.91 ± 0.03). Heart rates during the submaximal exercise control trials averaged 172 ± 3 bts \cdot min $^{-1}$ and were significantly increased to 178 ± 4 bts \cdot min $^{-1}$ by breathing the smoke (Fig. 2). RPE was also increased during the smoke trials from 11.8 ± 0.3 to 13.8 ± 1.0 units (Fig. 2). Ventilation was similar for both trials as was $P_{ET}CO_2$ and P_{ETO_2} (Table 1).

At rest, inhalation of smoke significantly increased the average heart from the normal of 81 ± 3 bts \cdot min $^{-1}$ to 90 ± 4 bts \cdot min $^{-1}$ (Fig. 3). Resting oxygen uptake was 0.23 ± 0.03 l \cdot min $^{-1}$ for the controls and was unaffected by the smoke (0.22 ± 0.02 l \cdot min $^{-1}$). Resting ventilation was not altered by the presence of smoke, nor was CO_2 output or R value. The presence of smoke raised the carboxyhemoglobin hemoglobin levels of the non-smokers from a pre-level of 1.1% to 2.2% at the end of exercise.

Discussion

The results of this investigation support the contention that involuntary inhalation of residual smoke lowers maximal exercise capacity and alters submaximal exercise response. The reduction in maximal performance is directly attributable to the carbon monoxide from the inhaled smoke binding with the hemoglobin (COHB) and reducing the oxygen carrying capacity. Rowell (1969) and Lamb (1984) have suggested that a maximal

Table 1. Respiratory responses during resting, submaximal and maximal exercise with and without the presence of smoke (Mean \pm SEM)

	Rest		Submaximal exercise		Maximal exercise	
	No Smoke	Smoke	No Smoke	Smoke	No Smoke	Smoke
Ventilation (l \cdot min $^{-1}$; BTPS)	6.97 0.64	6.13 0.52	50.04 2.33	52.51 3.39	72.82 5.52	71.51 5.42
\dot{V}_E/\dot{V}_{O_2} ratio	30.8 1.1	28.0 1.4	27.5 2.1	28.4 2.2	30.5 1.9	33.5 2.2
End-tidal CO_2 (mm Hg)	34.9 0.8	35.4 0.7	33.1 1.2	31.8 1.5	30.9 0.9	33.5 1.3
End-tidal O_2 (mm Hg)	96.8 1.9	97.2 1.8	98.7 2.5	101.5 2.4	104.2 3.2	104.7 2.8

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exertional levels, up to 90% of the oxygen carrying capacity may be needed. If the smoke reduces this capacity, the muscle cannot attain the high rate of aerobic metabolism unless cardiac output is further increased. Since maximal heart rates were similar during the control and smoke trials, the cardiovascular system seemed to be maximally taxed. Therefore, any reduction in the oxygen carrying capacity would reduce maximal aerobic performance ($\dot{V}O_2 = \dot{Q} \times (a-v)O_2$).

The greater lactate at a lower $\dot{V}O_2$ during the smoke trials indicates a greater reliance on anaerobic metabolism. This alteration is attributable to the increased COHB levels. As a consequence of the anaerobiosis, an increase in CO_2 output via the bicarbonate buffer system would be expected. Our results support this response as CO_2 production at a given $\dot{V}O_2$ was higher during the smoke trials. Therefore, the combined effect of the reduced oxygen carrying capacity and the concomitant increase in lactate resulted in a reduction in subjective maximal aerobic power and the duration of exercise during the residual smoke trials.

Examination of our maximal results suggest that the subjects may not have attained true maximal capacity during the smoke or control trials. Although maximal heart rate responses were within normal range for the subject's respective ages, other indicators, such as R values over 1.10 or lactates over 8 mM (Lamb 1984) suggest that did not reach maximum. Since the subjects were relatively untrained and since the protocol involved approximately 20 min of high intensity exercise before the incremental work to maximum, it is likely that they fatigued before attaining maximal capacity. We did note that the $\dot{V}O_2$ during the screening was higher and R values were above 1.10. Therefore, we believe that the efforts during the control and smoke trials represent the best subjective effort they could attain.

Passive inhalation of cigarette smoke significantly altered the submaximal heart rate and R values. Heart rates were increased by approximately 6 $bts \cdot min^{-1}$ in an attempt to improve cellular oxygenation, as a result of the elevated COHB. The increased R value during submaximal exercise smoke trials may indicate a shift toward greater utilization of glucose or glycogen (as a result of the reduced oxygen). The shift may not be important during short periods of exercise, but during prolonged exercise the carbohydrate stores could become depleted resulting in an earlier onset of fatigue (Karlsson 1979). The possibility also exists that the elevated R was a passive result of CO_2 produced by the cigarettes.

Passive inhalation of cigarette smoke resulted in a 1% increase in carboxyhemoglobin levels of our non-smokers. Personal communications with the United States Environmental Protection Agency have indicated that the carboxyhemoglobin levels of the present investigation are representative of breathing air from a smoke filled room. Also, Russell (1973) noted that spending 78 min in a smoke filled room resulted in carboxyhemoglobin levels increasing an average of one percent. Therefore, we are confident that our results are representative of normal passive inhalation of sidestream, or residual smoke and not the direct inhalation from a cigarette.

The subject's awareness of the smoke was reduced by injecting it into the air line from a hidden machine. The subjects never came off the mouthpiece or removed the noseclips, thus preventing smelling the smoke. All of the smokers could tell when they were breathing the smoke but none of the non-smokers knew for certain. In fact, two of the smokers told us the brand name of the cigarettes! Therefore, it seems that the smokers were more sensitive to the presence of the smoke, in agreement with Maksud and Baron (1980).

Although the number of subjects in the study were relatively small, the results imply that passive inhalation of cigarette smoke has a significant detrimental effect on exercise performance, specifically, by reducing maximal aerobic power and endurance capacity and increasing the need for anaerobiosis. The results suggest people participating in activities that demand high intensity for a prolonged period should avoid smoke filled areas.

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Aronow, W.S., "Effect of Passive Smoking on Angina Pectoris," New England Journal of Medicine 299(1): 21-24, 1978.

Ten subjects were used, all of whom were coronary heart disease patients in whom exercise would induce angina. They were exposed to ETS either in a ventilated or an unventilated room. They were then given an exercise test using a bicycle ergometer. Aronow reported that ETS exposure produced a variety of adverse cardiovascular changes, but most importantly a decrease in the duration of exercise until angina. This effect was greater in an unventilated room than in a ventilated room.

Comment

The 1978 Aronow report is widely recognized in the literature as being highly questionable. Even the 1986 Surgeon General's Report discussed criticisms of this report in terms of the endpoint, angina, being based on subjective evaluation and the lack of control for a variety of factors.

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EFFECT OF PASSIVE SMOKING ON ANGINA PECTORIS

WILBERT S. ARONOW, M.D.

Abstract: The effect of passive smoking on exercise-induced angina in a well ventilated and in an unventilated room was evaluated in 10 patients with angina. Patients exposed to 15 cigarettes smoked within two hours in a well ventilated room or an unventilated room increased their resting heart rate, systolic and diastolic blood pressure, and venous carboxyhemoglobin and decreased their heart rate and systolic blood pressure at angina. Patients exposed to passive smoking in an unventilated room had a larger in-

crease in resting heart rate, systolic and diastolic blood pressure, and venous carboxyhemoglobin and a greater reduction in heart rate and systolic blood pressure at angina. The duration of exercise until angina was decreased 22 per cent after passive smoking in a well ventilated room ($P < 0.001$), and decreased 38 per cent after passive smoking in an unventilated room ($P < 0.001$). Passive smoking aggravates angina pectoris. (N Engl J Med 299:21-24, 1978)

PASSIVE smoking is the breathing of smoke-containing air composed of mainstream smoke exhaled by smokers and of sidestream smoke, which leaves the burning end of the tobacco product during puff intermissions. The amount of smoke produced, the depth of inhalation on the part of the smoker, the ventilation available for the removal or dispersion of the smoke, the nearness of the nonsmoker to the smoker and the duration of the exposure to the pollutants in tobacco smoke influence the passive smoker's absorption of the atmospheric pollutants caused by smoking.¹

In patients with angina pectoris, anginal pain develops sooner after exercise when they have smoked high-nicotine cigarettes,² low-nicotine cigarettes³ or non-nicotine cigarettes.⁴ The effect of passive smoking on duration of exercise until angina pectoris also needed to be investigated. Therefore, I performed a randomized study evaluating the effect of passive smoking in a ventilated room and in an unventilated room on duration of exercise until the onset of angina pectoris. The data from this study are reported below.

MATERIALS AND METHODS

Ten men, with a mean age of 54.3 ± 8.1 years (± 1 S.D.), who had classic stable exertional angina pectoris and angiographic evidence of severe coronary-artery disease with > 75 per cent narrowing of at least one major coronary vessel were subjects. Eight subjects were ex-smokers. Two subjects smoked two to four cigarettes daily but did not smoke for at least 16 hours before the study or during the study on each of the three study mornings. After careful explanation of the risks involved, written informed consent was obtained from all 10 men with angina pectoris who participated in this study. The subjects understood the experimental design. Care was taken during the informed-consent discussion not to introduce psychological factors related to the risk of passive smoking.

The 10 subjects were familiarized with the equipment and the procedures and practiced exercising upright on a Collins* constant-load bicycle ergometer before the study began. The study was performed on three consecutive mornings.

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*Warren E. Collins, Inc., Braintree, MA.

On three successive study mornings, at 8 o'clock, with the subject in the fasting state, venous blood was drawn and analyzed for carboxyhemoglobin and hemoglobin levels with a 182 Co-Oximeter†. Then, Leads 2 and V_1 were simultaneously recorded with an electrocardiograph with the patient sitting on the bicycle ergometer. The resting heart rate was obtained from this electrocardiogram. The resting blood pressure was then measured with a mercury sphygmomanometer.

Each subject then exercised upright on the bicycle ergometer with a progressive work load until the onset of angina pectoris, and the duration of exercise was recorded with a stopwatch. The patient was monitored by telemetry with Leads 2 and V_1 throughout exercise. An electrocardiogram with Leads 2 and V_1 simultaneously was recorded at the onset of angina pectoris. The heart rate was obtained from this electrocardiogram. The blood pressure was recorded at the onset of angina pectoris, with the patient continuing to exercise until the blood pressure was obtained.

In a room 3.51 meters (11.5 ft) long, 3.20 meters (10.5 ft) wide and 2.74 meters (9.0 ft) high, near the research exercise laboratory, the subject then sat with three asymptomatic volunteers for two hours. The patient and asymptomatic volunteers talked, read newspapers or magazines or listened to music. On one morning, the asymptomatic volunteers did not smoke. On a second morning, each of the asymptomatic volunteers smoked five cigarettes, his or her own brand, during the two hours. The room was well ventilated, with a ventilation rate of 11.4 volumetric air changes per hour. On a third morning, each of the asymptomatic volunteers smoked five cigarettes, his or her own brand, during the two hours, with the room unventilated. The order of exposure of the patients with angina pectoris to no smoking, smoking in a well ventilated room or smoking in an unventilated room was randomized.

After exposure to no smoking for two hours, exposure to passive smoking for two hours in a well ventilated room, and exposure to passive smoking for two hours in an unventilated room, the patient sat on the bicycle ergometer and had an electrocardiogram with Leads 2 and V_1 simultaneously recorded. The heart rate was measured from this electrocardiogram. Then, the blood pressure was recorded with a mercury sphygmomanometer. Venous blood was next drawn and analyzed for carboxyhemoglobin and hemoglobin levels.

Subsequently, the patient exercised upright on the bicycle ergometer until the onset of angina pectoris, and the duration of exercise was recorded with a stopwatch. An electrocardiogram with Leads 2 and V_1 was simultaneously recorded at the onset of angina pectoris. The heart rate was obtained from this electrocardiogram. The blood pressure was recorded at the onset of angina pectoris, with the patient continuing to exercise until the blood pressure was obtained. The physician who performed the exercise tests knew whether the patients were exposed to no smoking, smoking in a well ventilated room or smoking in an unventilated room.

†Instrumentation Laboratory, Inc., Lexington, MA.

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In the asymptomatic volunteer smokers venous blood was drawn and analyzed for carboxyhemoglobin before and after smoking of five cigarettes each during two hours. The same smoking volunteers were present for the successive study mornings. Written informed consent was obtained from these volunteers.

The data were analyzed with Student's *t*-test for correlated means.

RESULTS

Table 1 indicates the duration of exercise in seconds until the onset of angina pectoris for each patient and the mean exercise duration \pm 1 S.D. in the three control periods, after exposure to no smoking, after exposure to smoking in a well ventilated room and after exposure to smoking in an unventilated room. Table 1 also presents the statistical analysis of the differences shown.

Table 2 shows the resting mean heart rate, systolic and diastolic blood pressure, product of systolic blood pressure \times heart rate/100, and venous carboxyhemoglobin \pm 1 S.D. in the three control periods, after exposure to no smoking, after exposure to smoking in a well ventilated room and after exposure to smoking in an unventilated room. Table 2 also presents the statistical analysis of the differences shown.

Table 3 indicates the mean heart rate, systolic and diastolic blood pressure, product of systolic blood pressure \times heart rate/100 and amount of exercise-induced ST-segment depression at the onset of angina pectoris \pm 1 S.D. in the three control periods, after ex-

posure to no smoking, after exposure to smoking in a well ventilated room and after exposure to smoking in an unventilated room. Table 3 also presents the statistical analysis of the differences shown.

The mean venous carboxyhemoglobin in the volunteer smokers rose from 5.87 ± 0.90 per cent before to 9.75 ± 1.05 per cent after smoking in the well ventilated room ($P < 0.001$). The mean venous carboxyhemoglobin in the volunteer smokers rose from 5.92 ± 0.95 per cent before smoking in the unventilated room to 9.83 ± 1.19 per cent after smoking in the unventilated room ($P < 0.001$).

Premature ventricular beats were not recorded in the electrocardiogram before exercise or after exercise in any patient during the three control periods or after exposure to no smoking or to passive smoking in a well ventilated room. After exposure to passive smoking in an unventilated room, one of 10 patients (10 per cent) had three premature ventricular beats per minute recorded in the electrocardiogram before exercise, and three of 10 patients (30 per cent) had premature ventricular beats recorded in the electrocardiogram after exercise. One patient had seven premature ventricular beats immediately after exercise, with premature ventricular beats lasting for five minutes; one patient had 10 premature ventricular beats per minute immediately after exercise, with premature ventricular beats lasting for eight minutes, and one patient had 12 premature ventricular beats per minute immediately after exercise, with premature ventricular beats lasting for 14 minutes.

Table 1. Duration of Exercise until Angina in the Control Periods* and after Exposure to No Smoking, Smoking in a Well Ventilated Room and Smoking in an Unventilated Room.

CASE No.	DURATION OF EXERCISE (SEC)					
	EXPOSURE TO NO SMOKING — CONTROL	EXPOSURE TO NO SMOKING	EXPOSURE TO SMOKING IN WELL VENTILATED ROOM — CONTROL	EXPOSURE TO SMOKING IN WELL VENTILATED ROOM	EXPOSURE TO SMOKING IN UNVENTILATED ROOM — CONTROL	EXPOSURE TO SMOKING IN UNVENTILATED ROOM
1.	193	217	191	149	202	127
2	206	214	203	169	189	130
3	188	197	181	145	192	128
4	375	412	400	306	387	230
5	204	199	211	170	196	132
6	287	310	304	243	312	198
7	221	215	213	158	232	135
8	216	223	207	155	209	124
9	195	208	186	144	200	129
10	231	224	227	172	218	125
Mean \pm SD	231.6 \pm 57.9	241.9 \pm 67.8	232.3 \pm 68.4	181.1† \pm 52.4	233.7 \pm 64.8	145.8† \pm 36.9

*Control values were measured on each of the three days before exposure or non-exposure to smoke.

† $P < 0.001$ for exposure to smoking in well ventilated room minus respective control as compared to exposure to no smoking minus respective control or for exposure to smoking in unventilated room minus respective control as compared to exposure to no smoking minus respective control.

‡ $P < 0.001$ for exposure to smoking in unventilated room minus respective control as compared to exposure to smoking in well ventilated room minus respective control.

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Table 2. Resting Mean Heart Rate, Systolic and Diastolic Blood Pressure, Product of Systolic Blood Pressure \times Heart Rate/100 and Venous Carboxyhemoglobin in the Control Periods and after Exposure to No Smoking, Smoking in a Well Ventilated Room and Smoking in an Unventilated Room (± 1 S.D.).

MEASUREMENT*	EXPOSURE TO NO SMOKING — CONTROL	EXPOSURE TO NO SMOKING	EXPOSURE TO SMOKING IN WELL VENTILATED ROOM — CONTROL	EXPOSURE TO SMOKING IN WELL VENTILATED ROOM	EXPOSURE TO SMOKING IN UNVENTILATED ROOM — CONTROL	EXPOSURE TO SMOKING IN UNVENTILATED ROOM
Heart rate (beats/min)	72.4 ± 7.7	70.6 ± 7.1	72.1 ± 7.3	77.2 $\pm 6.8^{\dagger}$	72.9 ± 7.8	80.5 $\pm 7.5^{\ddagger}$
SBP (mm Hg)	122.8 ± 4.9	122.0 ± 4.5	122.6 ± 5.6	127.5 $\pm 5.9^{\dagger}$	123.2 ± 4.4	130.7 $\pm 4.6^{\ddagger}$
DBP (mm Hg)	79.2 ± 2.5	78.6 ± 2.5	79.4 ± 3.3	82.9 $\pm 3.1^{\dagger}$	79.8 ± 2.0	85.4 $\pm 1.8^{\ddagger}$
Heart rate \times SBP/100	89.0 ± 11.0	86.2 ± 9.6	88.4 ± 10.3	98.5 $\pm 10.1^{\dagger}$	89.8 ± 10.2	105.2 $\pm 10.2^{\ddagger}$
Carboxyhemoglobin (%)	1.29 ± 0.22	1.26 ± 0.18	1.25 ± 0.20	1.77 $\pm 0.16^{\dagger}$	1.30 ± 0.18	2.28 $\pm 0.15^{\ddagger}$

*SBP denotes systolic blood pressure & DBP diastolic blood pressure.

$^{\dagger}P < 0.001$ for exposure to smoking in well ventilated room minus respective control as compared to exposure to no smoking minus respective control or for exposure to smoking in unventilated room minus respective control as compared to exposure to no smoking minus respective control.

$^{\ddagger}P < 0.001$ for exposure to smoking in unventilated room minus respective control as compared to exposure to smoking in well ventilated room minus respective control.

$^{\S}P < 0.005$ for exposure to smoking in unventilated room minus respective control as compared to exposure to smoking in well ventilated room minus respective control.

DISCUSSION

The data from this study clearly demonstrate that under the conditions of this experiment, passive smoking causes anginal pain to develop sooner after exercise. The duration of exercise until angina pectoris is also decreased more after passive smoking in an unventilated room than after passive smoking in a ventilated room.

Smoking high-nicotine^{2,3,6} or low-nicotine^{1,3} cigarettes causes an increase in resting heart rate and in systolic and diastolic blood pressure in patients with angina pectoris, increasing their myocardial oxygen

demand. This increase in heart rate and in blood pressure does not occur after smoking of non-nicotine cigarettes^{4,5} or after breathing of carbon monoxide.^{6,7} The increase in heart rate and systolic and diastolic blood pressure at rest in our patients with angina pectoris after exposure to passive smoking was presumably due to absorption of nicotine.

Russell and Feyerabend⁸ showed that after normal exposure to tobacco smoke, nicotine was present in urine collected during the early afternoon in 26 of 27 nonsmokers (96 per cent). The mean urinary nicotine level of these 27 nonsmokers was 10.7 ng per milliliter.

Russell and Feyerabend⁸ also had 12 nonsmokers

Table 3. Mean Heart Rate, Systolic and Diastolic Blood Pressure, Product of Systolic Blood Pressure \times Heart Rate/100 and Exercise-induced ST-Segment Depression at Onset of Angina in the Control Periods and after Exposure to No Smoking, Smoking in a Well Ventilated Room and Smoking in an Unventilated Room (± 1 S.D.).

MEASUREMENT*	EXPOSURE TO NO SMOKING — CONTROL	EXPOSURE TO NO SMOKING	EXPOSURE TO SMOKING IN WELL VENTILATED ROOM — CONTROL	EXPOSURE TO SMOKING IN WELL VENTILATED ROOM	EXPOSURE TO SMOKING IN UNVENTILATED ROOM — CONTROL	EXPOSURE TO SMOKING IN UNVENTILATED ROOM
Heart rate (beats/min)	128.7 ± 5.6	129.7 ± 5.6	128.9 ± 4.4	122.8 $\pm 4.7^{\dagger}$	128.4 ± 5.3	119.9 $\pm 5.0^{\ddagger}$
SBP (mm Hg)	156.4 ± 7.6	157.2 ± 7.4	156.1 ± 7.2	150.4 $\pm 7.8^{\dagger}$	155.6 ± 6.9	147.4 $\pm 7.8^{\ddagger}$
DBP (mm Hg)	80.2 ± 3.3	79.8 ± 2.9	81.0 ± 2.2	81.5 ± 3.4	81.3 ± 3.1	81.8 ± 2.2
Heart rate \times SBP/100	201.4 ± 14.7	203.9 ± 14.0	201.2 ± 11.8	184.7 $\pm 12.3^{\dagger}$	199.8 ± 11.9	176.7 $\pm 11.9^{\ddagger}$
ST-segment depression (mm)	1.38 ± 0.24	1.35 ± 0.24	1.33 ± 0.21	1.40 ± 0.24	1.33 ± 0.26	1.45 ± 0.26

*SBP denotes systolic blood pressure & DBP diastolic blood pressure.

$^{\dagger}P < 0.001$ for exposure to smoking in well ventilated room minus respective control as compared to exposure to no smoking minus respective control or for exposure to smoking in unventilated room minus respective control as compared to exposure to no smoking minus respective control.

$^{\ddagger}P < 0.001$ for exposure to smoking in unventilated room minus respective control as compared to exposure to smoking in well ventilated room minus respective control.

sit for an average of 78 minutes among smokers in an unventilated smoke-filled room with dimensions of 4.57 by 3.66 by 2.44 meters (15 by 12 by 8 ft). The smoke was produced by smoking or burning of 80 cigarettes and two cigars and caused a mean carbon monoxide level of 38 ppm in the room air. Urine specimens collected 15 minutes after the nonsmokers had left the smoke-filled room revealed a mean urinary nicotine level of 80 ng per milliliter.

Smoking high-nicotine,^{9,10} low-nicotine¹¹ or non-nicotine cigarettes¹² causes an increased carboxyhemoglobin level, which reduces the amount of oxygen available to the myocardium. Numerous studies have documented the harmful effects of carbon monoxide in patients with coronary heart disease.^{6-8,10-12} The decrease in product of systolic blood pressure times heart rate at the onset of angina pectoris after passive smoking in the study reported above indicates a probable decrease in oxygen delivery to the myocardium.

A number of investigations have shown the exposure of passive smokers to carbon monoxide levels¹³⁻¹⁸ that may cause adverse effects in patients with coronary heart disease. The data from this study also indicate that passive smoking causes an increase in carboxyhemoglobin — more after passive smoking in an unventilated room than after passive smoking in a ventilated room.

Premature ventricular beats occurred after exercise in three of 10 patients exposed to passive smoking in an unventilated room. The increase in sudden death from coronary heart disease in cigarette smokers¹⁹ may be related to lowering of the threshold for ventricular fibrillation by nicotine^{20,21} or carbon monoxide^{22,23} during an episode of myocardial ischemia.

Finally, in addition to carbon monoxide and nicotine, other components of tobacco smoke, including oxides of nitrogen and hydrogen cyanide and possibly psychologic factors, may have contributed to the decrease in exercise performance observed in these patients with heart disease after passive smoking through effects on the cardiovascular or respiratory systems. For example, do the oxides of nitrogen inhaled in tobacco smoke interfere with myocardial oxygen delivery? This possibility needs to be investigated.

I am indebted to Clifford Rousseve and Paul Troop for technical assistance.

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Khalfen, E.Sh. and Klochkov, V.A., "Effect of 'Passive' Smoking on the Physical Load Tolerance of Coronary Heart Disease Patients," Ter. Arkh. 5: 112-115, 1987. [Uncertified translation]

Khalfen and Klochkov exposed both smoking and smoking subjects to ETS, and then evaluated their exercise performance and cardiovascular reactions on a bicycle ergometer. Ten of the 81 subjects were healthy. The other 71 were heart disease patients, suffering from effort (exercise) induced angina. In one of the conditions, the ETS exposure was modified for some of the subjects by ventilating the room for 10 minutes twice during the two hour period.

For healthy subjects, the authors reported no statistically significant effect of ETS on bicycle ergometer testing. However, for angina patients, the ETS exposure significantly reduced exercise performance, onset of angina, and other cardiovascular parameters. The adverse effect of ETS exposure was reported to be somewhat less for smokers than for nonsmokers, at least for those with the less severe cases of angina. For more serious heart disease cases, the adverse effect was reported to be essentially identical regardless of whether they were smokers or not. The ventilation condition was reported not to prevent these adverse effects of ETS exposure.

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Comment

It is almost impossible to "blind" either the experimenter or the subjects in an experimental study of ETS exposure. Because of the distinctive olfactory and perhaps other sensory qualities of ETS, a subject will be aware of the exposure conditions and hence subjective reactions can influence the results. This is especially of concern in a study where one of the major dependent variables is subjective, in this case, the experience of pain (angina).

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таким образом, полученные нами данные на достаточно большом и представительном материале показывают связь типичного питания с липопротеинами плазмы крови в реальных условиях в популяции. Показательно, что в результате нашего исследования наиболее выраженная зависимость apo B и A-I отмечается от жирового компонента рациона и от показателей массы тела.

Полученная информация может быть полезной для выработки обоснованных диетических подходов профилактики атерогенных сдвигов в системе липопротеинов плазмы крови в популяции.

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ВЛИЯНИЕ «ПАССИВНОГО» КУРЕНИЯ НА ТОЛЕРАНТНОСТЬ К ФИЗИЧЕСКОЙ НАГРУЗКЕ У БОЛЬНЫХ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

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В настоящее время не вызывает сомнения, что курение способствует развитию ишемической болезни сердца (ИБС) [1, 2, 4, 5]. Риск развития ИБС увеличивается в 2—3 раза для лиц, выкуривающих более 1 пачки сигарет в день [3, 10]. Частота развития инфаркта миокарда и внезапной смерти прямо связана с курением [5, 7]. В то же время прекращение курения снижает риск развития повторного инфаркта миокарда и внезапной смерти на 20—50 % [11, 12].

При проведении велоэргометрической пробы выявлена отрицательная корреляция между курением сигарет и толерантностью к физической нагрузке [1]. Доказана связь коронарографи-

чески подтвержденного спазма венечных артерий и усиления агрегации тромбоцитов с курением [9].

Однако подавляющее большинство исследований проведено среди курящих. Между тем показано [8, 11], что даже «пассивное» курение, т. е. просто пребывание в накуренном помещении и вдыхание табачного дыма, оказывает выраженное отрицательное влияние на состояние сердечно-сосудистой системы. D. Mackenzi [8] считает, что ежегодно около тысячи англичан погибают от последствий «пассивного» курения.

Вопрос о «пассивном» курении еще недостаточно изучен. В связи с этим нами проведено

исследования; целью которого была оценка влияния «пассивного» курения на показатели велоэргометрической пробы у больных ИБС.

Под наблюдением находился 81 человек: 10 практически здоровых лиц в возрасте от 25 до 48 лет (средний возраст 38 лет) и 71 больной стенокардией напряжения в возрасте от 31 года до 63 лет (средний возраст 49 лет). Все обследованные были мужчины.

Среди больных стенокардией курящих (выкуривающих в среднем 1 пачку сигарет в день) было 33, некурящих — 38. Среди здоровых лиц курящих было 5, некурящих — 5.

У 39 больных ИБС имелась стенокардия напряжения I и II функциональных классов, у 32 больных — стенокардия напряжения III и IV функциональных классов. 15 человек перенесли в прошлом трансмуральный инфаркт миокарда. Гипертонической болезнью II стадии страдали 10 человек.

Все курящие в течение 2 ч до проведения велоэргометрической пробы воздерживались от курения. За сутки до исследования всем больным отменяли антиангинальные средства, за исключением таблеток нитроглицерина.

Велоэргометрическую пробу проводили в положении сидя на велоэргометре «Сименс-Элема» с регистрацией ЭКГ в 3 отведениях по Небу на струйном полиграфе «Мингограф-82». Использовали ступенчато возрастающую непрерывную нагрузку длительностью 3 мин с последовательным приращением мощности на 25 Вт. Причиной прекращения велоэргометрической пробы служили достижение субмаксимальной частоты пульса, смещение сегмента ST горизонтального и косинусоидального типа ниже изолинии на 1 мм и более, возникновение типичного приступа стенокардии, купирующегося приемом нитроглицерина, инверсия зубца T в 2 и более отведениях.

При оценке велоэргометрической пробы учитывали следующие показатели: толерантность к нагрузке (в ваттах), двойное произведение — ДП (в условных единицах) и отношение ДП к мощности нагрузки (ДП/Вт).

Исследование проводили в комнате площадью 24 м², высотой 3,2 м, в которой был установлен велоэргометр. Вначале в обычных условиях обследованным проводили велоэргометрическую пробу по описанной выше методике. Затем в помещении выкуривали 8 сигарет в течение 2 ч (по 1 сигарете каждые 15 мин). Все это время обследованные находились в комнате: сидели в кресле, читали журналы, беседовали, играли в шашки. После 2-часового пребывания в накуреном помещении проводили повторную велоэргометрическую пробу.

Для 15 обследованных проба была модифицирована: в течение 2 ч пребывания больных в накуреном помещении его дважды (в конце каждого часа) проветривали в течение 10 мин через фрамугу площадью 0,5 м².

Для того чтобы установить, не влияет ли проведение предварительной велоэргометрической пробы на ее показатели при повторном проведении пробы через 2 ч, у 10 больных стенокардией напряжения II—IV функционального класса (средний возраст 48 лет) толерантность к нагрузке исследовали дважды с интервалом 2 ч после пребывания в описанном выше помещении, в котором не курили. Оказалось, что исходная толерантность к нагрузке в группе составила в среднем $62,5 \pm 1,4$ Вт, а при повторном исследовании через 2 ч — $70 \pm 2,0$ Вт (у 3 больных стенокардией напряжения при повторном проведении пробы отмечено повышение толерантности на 1 ступень — 25 Вт).

Проведенные исследования подтверждают правомерность использования парных велоэргометрических нагрузок, о чем свидетельствует и широкий опыт их использования у нас в стране и за рубежом при подборе больным антиангинальных препаратов.

Проведенные исследования показали, что в группе практически здоровых лиц толерантность к нагрузке до пребывания в накуреном помещении в среднем составила $192 \pm 5,5$ Вт, ДП — $246 \pm 7,2$ усл. ед., а показатель ДП/Вт — $1,3 \pm 0,04$. После «пассивного» курения толерантность к нагрузке в этой группе составила $197 \pm 5,7$ Вт, ДП — $238 \pm 7,1$ усл. ед. и ДП/Вт — $1,2 \pm 0,03$. Таким образом, статистически значимых различий в показателях велоэргометрической пробы до и после «пассивного» курения у здоровых людей выявлено не было.

У больных ИБС отдельно изучали результаты пробы с «пассивным» курением без проветривания помещения (1-я группа) и при кратковременном проветривании комнаты (2-я группа).

В 1-й группе больных стенокардией напряжения средняя толерантность к нагрузке до проведения пробы с «пассивным» курением в непроветриваемом помещении составила $87 \pm 2,6$ Вт, а после пробы — $63 \pm 1,8$ Вт ($p < 0,01$). Причинами прекращения велоэргометрической пробы как до, так и после курения у 21 человека был приступ стенокардии напряжения, у 18 — смещение сегмента ST ниже изолинии на 1 мм и более, у 4 — инверсия зубца T и у 3 — достижение субмаксимальной частоты сердечных сокращений.

Под влиянием «пассивного» курения у больных стенокардией напряжения снижалась толерантность к нагрузке, уменьшалось ДП и увеличивалось отношение ДП/Вт (табл. 1). Указанные изменения были значительно более резко выражены у больных стенокардией напряжения III—IV функционального класса по сравнению с больными стенокардией I—II функционального класса. Так, у курящих больных стенокардией напряжения I—II функционального класса толерантность к нагрузке уменьшилась в среднем на 17 %, а у курящих больных стенокардией на-

Таблица 1

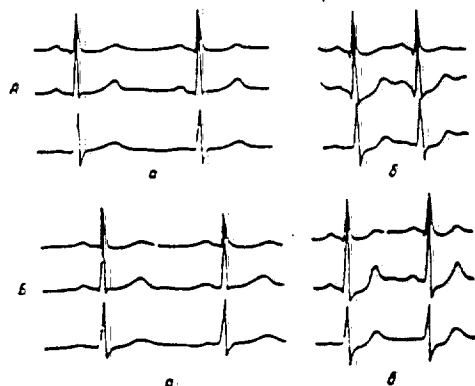
Показатели велоэргометрической пробы у больных стенокардией напряжения до (А) и после (Б) 2-часового пребывания в непроветриваемом накуренном помещении ($M \pm m$)

Функциональный класс стенокардии напряжения	Показатель	Некурящие			Курящие		
		А	Б	р	А	Б	р
I—II	Толерантность к нагрузке, Вт	109 \pm 3,9	90 \pm 2,8	$\leq 0,01$	125 \pm 3,8	116 \pm 3,5	$\leq 0,05$
	ДП, усл. ед.	194 \pm 5,7	182 \pm 5,5	$\geq 0,05$	183 \pm 5,4	177 \pm 5,3	$\geq 0,05$
	ДП/Вт	1,8 \pm 0,06	2,0 \pm 0,06	$\geq 0,05$	1,5 \pm 0,05	1,5 \pm 0,05	$\geq 0,05$
III—IV	Толерантность к нагрузке, Вт	57 \pm 1,6	30 \pm 1,0	$\leq 0,01$	50 \pm 1,5	28 \pm 0,8	$\leq 0,01$
	ДП, усл. ед.	148 \pm 4,3	126 \pm 3,6	$\leq 0,01$	129 \pm 3,5	115 \pm 3,5	$\leq 0,01$
	ДП/Вт	2,6 \pm 0,07	4,2 \pm 0,1	$\leq 0,01$	2,6 \pm 0,07	4,0 \pm 0,09	$\leq 0,01$

пряжения III—IV функционального класса — на 47 %.

Толерантность к физической нагрузке и ДП после пребывания в накуренном помещении отчетливо снижались вне зависимости от того, курит сам больной или нет. Однако у курящих больных «пассивное» курение вызывало несколько меньшее снижение велоэргометрических показателей, чем у некурящих. Следует отметить, что такое различие отмечалось у больных с более легким течением стенокардии напряжения, тогда как больные стенокардией напряжения III и IV функциональных классов реагировали на «пассивное» курение практически одинаково независимо от того, являются они курильщиками или нет.

Больной Е., 47 лет. Диагноз: ИБС, стенокардия напряжения III функционального класса. Давящие боли за грудиной, иррадиирующие в левое плечо, возникают ежедневно при ходьбе, подъеме по лестнице. Боли в течение 2—3 мин проходят после прекращения движения или приема нитроглицерина. При коронарографическом исследовании выявлен 90 % стеноз правой коронарной артерии и



Динамика ЭКГ у больного Е., 47 лет, при проведении велоэргометрической пробы до (А) и после (Б) 2-часового пребывания в непроветриваемом накуренном помещении: а — ЭКГ в покое; б — ЭКГ во время проведения велоэргометрической пробы. Обращения в текст.

50 % стеноз огибающей ветви левой коронарной артерии. 27.06.85 проведена велоэргометрическая проба. В покое, до проведения пробы патологические изменения ЭКГ не выявлены.

При проведении велоэргометрической пробы до «пассивного» курения толерантность к нагрузке составила 75 Вт, ДП — 220 усл. ед., ДП/Вт — 2,9. Причина прекращения велоэргометрической пробы — приступ стенокардии и смещение сегмента ST в 2 отведениях ниже изолинии на 1 мм (см. рисунок).

После 2-часового пребывания в накуренном помещении проведена повторная велоэргометрическая проба. Толерантность к нагрузке на этот раз составила 60 Вт, ДП — 200 усл. ед., ДП/Вт — 4,0. Причина прекращения велоэргометрической пробы — приступ стенокардии и смещение сегмента ST в 2 отведениях ниже изолинии на 1,5 мм.

Таким образом, у больного, страдающего стенокардией напряжения III функционального класса, после «пассивного» курения уменьшилась толерантность к нагрузке, снизилось ДП и увеличилось ДП/Вт.

Во 2-й группе при проведении пробы с «пассивным» курением с кратковременным проветриванием помещения у больных стенокардией до «пассивного» курения средняя толерантность к нагрузке составила 89 \pm 2,5 Вт, после пробы — 63 \pm 1,7 Вт ($p < 0,01$). Причинами прекращения велоэргометрической пробы послужили приступ стенокардии напряжения, купирующийся приемом нитроглицерина (у 7), смещение сегмента ST на 1 мм ниже изолинии (у 6) и инверсия зубца T (у 2).

У больных отмечалось выраженное уменьшение толерантности к нагрузке, ДП и увеличение ДП/Вт. Двукратное в течение 2 ч 10-минутное проветривание накуренного помещения не предотвращало эффекта «пассивного» курения (табл. 2).

В нашем исследовании достаточно большое помещение было сравнительно не сильно задымлено — в нем было выкурено всего 8 сигарет за 2 ч. В действительности мы часто сталкиваемся со значительно большей концентрацией табачного дыма в помещении. Однако и при незначительной концентрации дыма в помещении «пассивное» курение оказало выраженное отрицательное влияние на всех обследованных больных ИБС, выразившееся

Таблица 2

Показатели велоэргометрической пробы у больных стенокардией напряжения до (А) и после (Б) 2-часового пребывания в некурящем, временно проветриваемом помещении ($M \pm m$)

Функциональный класс стенокардии напряжения	Показатель	Некурящие			Курящие		
		А	Б	Р	А	Б	Р
I—II	Толерантность к нагрузке, Вт	120 ± 3,3	105 ± 3,1	<0,01	113 ± 3,5	110 ± 3,3	>0,05
	ДП, усл. ед.	196 ± 5,7	183 ± 5,5	>0,05	190 ± 5,4	186 ± 5,2	>0,05
	ДП/Вт	1,6 ± 0,05	1,8 ± 0,06	>0,05	1,7 ± 0,06	1,9 ± 0,06	>0,05
III—IV	Толерантность к нагрузке, Вт	50 ± 1,4	25 ± 0,7	<0,01	50 ± 1,4	25 ± 0,8	<0,01
	ДП, усл. ед.	143 ± 4,2	118 ± 3,6	<0,01	137 ± 3,4	110 ± 2,9	<0,01
	ДП/Вт	2,9 ± 0,08	4,7 ± 0,1	<0,01	2,8 ± 0,07	4,0 ± 0,09	<0,01

ся в снижении толерантности к физической нагрузке, уменьшении ДП и увеличении ДП/Вт. При этом кратковременное проветривание помещения через фрамугу (а именно такое проветривание обычно характерно для бытовых и служебных помещений) не предотвращало эффекта «пассивного» курения.

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THE EFFECT OF "PASSIVE" SMOKING ON CHD PATIENTS

E. Sh. Khalifen, V. A. Kiselev

Summary

"Passive" smoking has been shown to produce a marked negative effect on CHD patients. Short-term airing of a room does not prevent a negative effect of "passive" smoking.

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УРОВЕНЬ МОЧЕВОЙ КИСЛОТЫ В КРОВИ У ЗДОРОВЫХ
И БОЛЬНЫХ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

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Актуальность первичной профилактики ишемической болезни сердца (ИБС) обусловила значительный интерес к изучению различных факторов риска этой патологии. Наряду с общепризнанными факторами риска ИБС (артериальная гипертензия, ожирение, дислипипротендемии — ДЛП) существуют такие, значение которых остается дискуссионным. К последним относятся и гиперурикемия (ГУР). Высказывается мнение о существовании связи между повышенным уровнем мочевой кислоты (МК) в крови и заболеваемостью ИБС [5, 15, 16, 20], показана боль-

шая частота ГУР среди больных атеросклерозом и ИБС [10, 12]. Ряд авторов считают, что связь ГУР с атеросклерозом опосредована через другие факторы риска [9, 22]. Так, непосредственно не участвуя в развитии атеросклеротического процесса, ГУР коррелирует с атерогенными ДЛП и другими факторами риска.

Изучение роли ГУР в патогенезе атеросклероза и ее значения как фактора риска затруднено тем, что используемые для определения уровня МК в крови методы характеризуются недостаточной точностью и специфичностью, что не по-

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EFFECT OF "PASSIVE" SMOKING ON THE PHYSICAL LOAD
TOLERANCE OF CORONARY HEART DISEASE PATIENTS

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Summary

"Passive" smoking has been shown to produce a marked negative effect on CHD patients. Short-term airing of a room does not prevent a negative effect of "passive" smoking.

Translated from Russian

NOTE: THIS IS NOT A
CERTIFIED TRANSLATION

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EFFECT OF "PASSIVE" SMOKING ON THE PHYSICAL LOAD TOLERANCE OF
CORONARY HEART DISEASE PATIENTS

By E. Sh. Khalfen and V.A. Klochkov

There is no doubt at the present time that smoking can promote the development of coronary heart disease (CHD) [1,2,4,5]. The risk of CHD is doubled or tripled in people who smoke more than one pack of cigarettes per day [3,10]. The incidence of a myocardial infarction and sudden death has been linked directly to smoking [5,7]. Furthermore, the risk of a second myocardial infarction and sudden death is reduced 20 to 50% [11,12] if the smoker stops smoking.

A negative correlation between cigarette smoking and tolerance to physical load has been found in bicycle ergometry tests [1]. A spasm confirmed by coronary angiography in the coronary arteries and intensification of thrombocyte aggregation have been linked with smoking [9].

However, the overwhelming majority of investigations have been carried out on smokers. Nevertheless, it has been shown [8,11] that even "passive" smoking, i.e., just being present in a smoky environment and breathing tobacco, has a strong negative effect on the state of the cardiovascular system. D. Makkenzi [8] believes that about a thousand English people die every year from the effects of "passive" smoking.

"Passive" smoking has not yet been investigated adequately. We have therefore performed a study aimed at evaluating the effect of "passive" smoking on the indices obtained in the bicycle ergometer test on CHD patients.

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We made observations on 81 people, 10 of whom were practically healthy and ranged from 25 to 48 years of age (average age 38) and 71 patients with angina of effort ranging from 31 to 63 years (average age 49). All the subjects were men.

The angina patients included 33 smokers (who smoked an average of one pack of cigarettes per day) and 38 nonsmokers. The healthy group included 5 smokers and 5 nonsmokers.

Thirty-nine CHD patients had functional class I and II angina of effort and 32 had class III and IV angina of effort. Fifteen had undergone a transmural myocardial infarction in the past and 10 suffered from stage II hypertensive disease.

All the smokers abstained from smoking for two hours before taking the bicycle ergometer test. All the patients refrained from using antianginal agents several days before the tests, except for nitroglycerine tablets.

The bicycle ergometer test was carried out with the subjects in a sitting position on a Simens-Elema bicycle ergometer, registering the EKG with three Nebo leads on a Mingography-82 current polygraph. A continuous load was employed lasting 3 minutes, increasing by consecutive steps of 25 W. The bicycle ergometer test was stopped when a submaximum pulse rate was reached, when the ST segment shifted horizontally or slanting downward 1 mm or more below the isolines, when a typical angina attack occurred, which was arrested by administration of nitroglycerine, or when the T wave was inverted in two or more of the traces.

In evaluating the bicycle ergometer test, we considered the

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following indices: tolerance to load (in Watts), the double product of DP (in arbitrary units) and the ratio of the DP to the power load (DP/W).

The bicycle ergometer was installed and the test conducted in a 24-m² room, 3.2 m high. The test was performed on the subjects at first under the usual conditions in accordance with the procedure described above. Then eight cigarettes were smoked in the room over a two-hour period (one cigarette every 15 minutes). The subjects were in the room for this entire period, sitting in a chair, reading magazines, talking, or playing checkers. A second bicycle ergometer test was performed after this two-hour period in the smoky room.

The test was modified for 15 of the subjects by ventilating the smoky room for 10 minutes through a 0.5-m² transome twice during their two-hour stay (at the end of each hour).

In order to determine whether or not the first bicycle ergometer test affected the indices of the second test two hours later, tolerance to load tests were made on class II and IV angina of effort patients (average age 48) twice, two hours apart, after they had been in the room described above but without any smoke. The original tolerance to load averaged 62.5 ± 1.4 W and tolerance in the second test after two hours was 70 ± 2.0 W (three angina of effort patients showed tolerances in the second test that were one step higher, by 25 W).

The tests confirmed the validity of using paired bicycle ergometer loads. The validity of such a test has been demonstrated by extensive experience in our country and abroad in grading patients who take antianginal preparations.

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The tests have shown that the tolerance to load in a group of practically healthy people before a stay in a smoky room averaged 192 ± 5.5 W, DP averaged 246 ± 7.2 arbitrary units, and the DP/W index was 1.3 ± 0.04 . After "passive" smoking, the tolerance to load in this group was 197 ± 5.7 W, DP was 238 ± 7.1 arbitrary units, and DP/W was 1.2 ± 0.03 . Thus, there were no statistically significant differences in the bicycle ergometer indices in healthy people and after "passive" smoking.

We made a separate analysis of the results of the "passive" smoking test in the CHD patients without room ventilation (Group 1) and in those with a short period of ventilation (Group 2).

The average tolerance to load in the Group 1 angina of effort patients was 87 ± 2.6 W before the "passive" smoking test in the unventilated room and 63 ± 1.8 W after the test ($p < 0.01$). The main reasons for stopping the bicycle ergometer test both before and after smoking were an attack of angina of effort in 21 people, a shift in the ST segment 1 mm or more below the isoline in 18, inversion of the T waves in four, and achieving a submaximal heart contraction rate in three.

"Passive" smoking in angina of effort patients results in a lower tolerance to load, a lower DP and a higher DP/W ratio (Table 1). These changes were much more pronounced in class III and IV angina of effort patients than in class I and II angina patients. Thus, smokers who were class I and II angina of effort patients showed a 17% decrease in tolerance to load, whereas class III and IV angina patients showed a decrease of 47%.

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TABLE 1. Bicycle ergometer test indices in patients with angina of effort: A) before the 2-hour stay in the unventilated smoke-filled room; B) after the 2-hour stay (M±m).

Functional class of angina of effort	Index	Nonsmokers			Smokers		
		A	B	p	A	B	p
III-IV	Tolerance to load, W	109±3.9	90±2.8	<0.01	125±3.8	116±1.5	<0.05
	DP, arbit. units	194±5.7	182±5.5	>0.05	183±5.4	177±5.3	>0.05
	DP/W	1.8±0.06	2.0±0.06	>0.05	1.5±0.05	1.5±0.05	>0.05
	Tolerance to load, W	57±1.6	30±1.0	<0.01	50±1.5	28±0.8	<0.01
	DP, arbit. units	148±4.3	126±3.6	<0.01	129±3.5	115±3.5	<0.01
	DP/W	2.6±0.07	4.2±0.1	<0.01	2.6±0.07	4.0±0.09	<0.01

*arbitrary units

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The tolerance to physical load and the DP after staying in the smoky room dropped distinctly whether or not the patient was a smoker. However, the drop in bicycle ergometer indices induced by "passive" smoking was somewhat lower in smokers than in nonsmokers. It should be pointed out that such a difference was detected in patients with more moderate angina of effort, whereas class III and IV angina of effort patients reacted almost identically to "passive" smoking whether they were smokers or not.

Patient E. Age 47. Diagnosis: CHD, functional class III angina of effort. Pressing chest pains radiating to the left shoulder appeared daily when walking or ascending a stairway. Pains lasted 2 to 3 minutes after he stopped moving or took nitroglycerine. The coronary angiography indicated 90% stenosis of the right coronary artery and 50% stenosis of the circumflex branch of the left coronary artery. A bicycle ergometer test was performed on June 27, 1985. No pathological changes in the EKG were detected at rest before the ergometer test.

The bicycle ergometer test before "passive" smoking gave a tolerance to load of 75 W, a DP of 220 arbitrary units, and a DP/W ratio of 2.9. The test was stopped because of an angina attack and a shift of the ST segment 1 mm below the isolines on two traces (see Figure 1).

A second ergometer test was performed after he had spent two hours in the smoke-filled room. This time tolerance to load was 50 W, DP 200 arbitrary units, and DP/W 4.0. The test was stopped because of an angina attack and a shift in the ST segment 1.5 mm below the isolines on the two traces.

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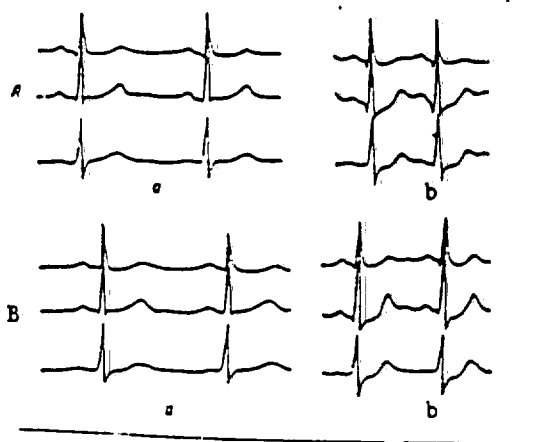


Figure 1. Dynamics of the EKG in patient E, age 47, during bicycle ergometer test: A) before 2-hour stay in unventilated smoke-filled room; B) after the 2-two stay. a) EKG at rest; b) EKG during the bicycle ergometer test. Explanation in text.

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Thus, load tolerance dropped, DP decreased, and DP/W increased in a patient suffering from class III angina of effort after "passive" smoking.

When the test was conducted by ventilating the room for a short time during the "passive" smoking period, the load tolerance of group 2 angina patients was 89 ± 2.5 W before "passive" smoking and 63 ± 1.7 W thereafter ($p < 0.01$). The bicycle ergometer tests were stopped because of an attack of angina of effort in 7 patients, followed by nitroglycerine administration; because of a shift in the ST segment 1 mm below the isolines in 6; and because of inversion of the T wave in 2.

A marked decrease in load tolerance and DP and an increase in DP/W were found in the patients. Two 10-minute ventilation periods in two hours did not prevent the effect of "passive" smoking (Table 2).

The rather large room used in this study was not very smoky, since only 8 cigarettes were smoked in two hours. In reality, we often encounter a much higher concentration of tobacco smoke in rooms. However, "passive" smoking in a room with a relatively low smoke concentration had a pronounced negative effect on all the subjects who were CHD patients, lowering tolerance to physical load, decreasing DP, and raising the DP/W ratio. A short ventilation period through a transom (which is usually typical of residential and service rooms) did not prevent "passive" smoking from exerting its effect.

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TABLE 2. Bicycle ergometer test indices in patients with angina of effort: A) before 2-hour stay in smoke-filled room ventilated for short time; B) after the 2-hour stay ($M \pm m$).

Functional class of angina of effort	Index	Nonsmokers			Smokers		
		A	B	p	A	B	p
III-IV	Tolerance to load, W	120 \pm 3.3	105 \pm 3.1	≤ 0.01	113 \pm 3.5	110 \pm 3.3	≥ 0.05
	DP, arbit. units	196 \pm 5.7	183 \pm 5.5	≥ 0.05	190 \pm 5.4	188 \pm 5.2	≥ 0.05
	DP/W	1.6 \pm 0.05	1.8 \pm 0.06	≥ 0.05	1.7 \pm 0.06	1.9 \pm 0.06	≥ 0.05
	Tolerance to load, W	50 \pm 1.4	25 \pm 0.7	≤ 0.01	50 \pm 1.4	25 \pm 0.8	≤ 0.01
	DP, arbit. units	143 \pm 4.2	118 \pm 3.6	≤ 0.01	137 \pm 3.4	110 \pm 2.9	≤ 0.01
	DP/W	2.9 \pm 0.08	4.7 \pm 0.1	≤ 0.01	2.8 \pm 0.07	4.0 \pm 0.09	≤ 0.01

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LEONE, A., MORI, L., BERTANELLI, F., FABIANO, P. AND FILIPPELLI, M., "INDOOR PASSIVE SMOKING: ITS EFFECTS ON CARDIAC PERFORMANCE," INTERNATIONAL JOURNAL OF CARDIOLOGY 33(2): 247-252, 1991

Cardiac performance during exercise testing was measured in 19 male nonsmokers, nine of whom were healthy and 10 of whom were myocardial infarction survivors. The subjects were tested twice, once while exposed to environmental tobacco smoke (leading to carbon monoxide concentrations of 30-35 ppm) and once without this exposure.

The authors reported that ETS exposure was associated with a decrease in peak exercise capacity in the myocardial infarction survivors, but not in the healthy subjects. For both groups of subjects, ETS exposure was associated with longer times to recovery of pre-exercise heart rates. ETS exposure during exercise testing was also associated with increases in expired air and plasma carbon monoxide concentrations, although there were some irregularities in the data pertaining to these comparisons. The authors concluded:

Cardiac response to the exercise is significantly worsened by passive smoke, especially in those subjects with previous myocardial infarction.

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CARDIO 01049

Indoor passive smoking: its effect on cardiac performance

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Leone A, Mori L, Bertanelli F, Fabiano P, Filippelli M. Indoor passive smoking: its effect on cardiac performance. *Int J Cardiol* 1991;33:247-252.

We studied 19 nonsmoker male volunteers, 9 healthy (mean age 30.5 ± 8.5), and 10 with previous myocardial infarction (mean age 53.8 ± 5.3), who underwent exercise stress testing twice: in a smoke-free environment and in a smoking environment (carbon monoxide concentration 30-35 ppm). We measured peak exercise power, time to recovery of pre-exercise heart rate, expired concentration of carbon monoxide and plasma carbon monoxide. Obtained data were compared by using *t*-test. $P < 0.05$ was statistically significant. Mean data observed in healthy people were as follows. Peak exercise power 220 ± 30 watts in a smoking environment versus 220 ± 30 in a smoke-free environment ($P > 0.05$). Time to recovery of pre-exercise heart rate 19 ± 4 minutes in a smoking environment versus 8.5 ± 4 in a smoke-free environment ($P < 0.01$). Expired concentration of carbon monoxide before exercise 2.3 ± 2.01 ppm versus 8.5 ± 1.6 ($P < 0.01$) after exercise in a smoking environment, and 2.3 ± 2 ppm before exercise versus 2.1 ± 1.9 after exercise in a smoke-free environment ($P > 0.05$). Plasma carbon monoxide before exercise $1.4 \pm 0.2\%$ versus 1.7 ± 0.4 after exercise in a smoking environment ($P > 0.05$), and $1.2 \pm 0.4\%$ before exercise versus 1.2 ± 0.4 in a smoke-free environment ($P > 0.05$). Corresponding measurements in survivors of infarction were as follows: peak exercise power 80 ± 25 watts versus 120 ± 20 ($P < 0.01$), time to recovery of pre-exercise heart rate 21 ± 2.5 minutes versus 12.3 ± 2.0 ($P < 0.01$), expired carbon monoxide 0.6 ± 0.2 ppm versus 5.2 ± 1.2 ($P < 0.01$) in a smoking environment and 1.2 ± 0.8 versus 1.3 ± 0.6 ($P > 0.05$) in a smoke-free environment, plasma carbon monoxide $1.2 \pm 0.16\%$ versus 2.3 ± 0.4 ($P < 0.01$) in a smoking environment and 1.2 ± 0.1 versus 1.2 ± 0.3 ($P > 0.05$) in a smoke-free environment. Cardiac response to the exercise is significantly worsened by passive smoke, especially in those subjects with previous myocardial infarction.

Key words: Passive smoking; Infarcted people

Introduction

Smoking interferes negatively with cardiac performance and is responsible for cardiac pathology

[1-4]. A strongly incriminating relationship between cigarette smoking and myocardial infarction has been shown by numerous studies [4-6], but a quantitative assessment of the alterations caused acutely by passive smoking on cardiac performance in healthy people and those with previous myocardial infarction has not yet been established.

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The purpose of this study was to investigate, quantitatively, the effects of passive smoking on cardiac performance of healthy people and those with previous myocardial infarction.

Materials and Methods

19 nonsmoker male volunteers (Table 1), 9 healthy aged from 17 years to 44 years (mean age with \pm standard deviation 30.5 ± 8.5 years), and 10 with previous myocardial infarction aged from 43 years to 59 years (mean age with \pm standard deviation 53.8 ± 5.3 years) were studied. The healthy people had no history of any illnesses at all. Their resting 12-lead electrocardiogram was normal. The subjects, who survived a first acute myocardial infarction, had had an anterior infarction in 5 cases and an inferior infarction in 5 cases. All subjects gave their informed consent to be included in this study.

The studied population underwent exercise stress testing on a bicycle ergometer twice: the first time, the subject performed the exercise in sixty cubic metres enclosed space not polluted by cigarette smoking. On the second occasion the ambient atmosphere was polluted by 30–35 ppm carbon monoxide concentration we reached by the combustion of 15 to 20 cigarettes within half an hour by using a switchover machine connected to a Programmable Infra-red Spectrophotometer at Variable Pathway (Wilks Mod. 80). This device allowed us to measure carbon monoxide concen-

tration and maintain it at the desired level during exercise stress testing. Each studied subject was test and control of himself.

During and after exercise, electrocardiographic leads V2–V6 were displayed continuously on a monitor scope, and once every minute a 12-lead electrocardiogram was recorded. Systolic blood pressure was also recorded with a sphygmomanometer during the last minute of the exercise. In each studied subject we assessed the peak exercise power, time to recovery of pre-exercise heart rate and carbon monoxide concentration of both expired air and plasma before and after exercise.

Statistical methods

Standard statistical methods were used. All data were compared by using the *t*-test. $P < 0.05$ was taken to denote statistical significance. The data are presented as means \pm SD.

Results

The results of this study are summarized on the Tables 2–5. Peak exercise power (Table 2) of healthy people ranged from 140 to 260 watts (mean 220 ± 30) in a smoke-free environment, and from 80 to 260 watts (mean 220 ± 30) in a smoking environment. The corresponding figures in survivors of infarction were 80 to 140 watts (mean 120 ± 20) in a smoke-free environment, and 60 to 120 watts (mean 80 ± 25) in a smoking environment, a statistically significant difference ($P < 0.01$).

Time to recovery of pre-exercise heart rate (Table 3) for healthy people was 4 to 18 minutes.

TABLE 1
Characteristics of the studied population.

Healthy people	
Number	9
Mean age (years)	30.5 ± 8.5
Sex (male)	9
No previous medical history	
Survivors of infarction:	
Number	10
Mean age (years)	53.8 ± 5.3
Sex (male)	10
Infarction	10
anterior	5
inferior	5

TABLE 2
Peak exercise power (watts), mean \pm SD, in the studied population.

Subjects	Smoking environment	Smoke-free environment	<i>t</i> -test
Healthy people	220 ± 30	220 ± 30	$P > 0.05$
Survivors of infarction	80 ± 25	120 ± 20	$P < 0.01$

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TABLE 3

Time to recovery of pre-exercise heart rate (minutes) mean \pm SD; in the studied population.

Subjects	Smoking environment	Smoke-free environment	t-test
Healthy people	19 \pm 4	8.50 \pm 4	$P < 0.01$
Survivors of infarction	21 \pm 2.5	12.30 \pm 2	$P < 0.01$

(mean 8.50 \pm 4) in a smoke-free environment, and 10 to 25 minutes (mean 19 \pm 4) in a smoking environment with a statistically significant difference ($P < 0.01$). The corresponding parameters in survivors of infarction ranged from 10 to 15 minutes (mean 12.3 \pm 2.0) in a smoke-free environment, and from 18 to 25 minutes (mean 21 \pm 2.50) in the environment polluted by cigarette smoke, a statistically significant difference ($P < 0.01$).

The results concerning the concentration of expired carbon monoxide are displayed in Table 4. In healthy volunteers there was no difference in the values prior to exercise between the smoking and smoke-free environments (2.3 \pm 2.01 versus 2.3 \pm 2.0 ppm). In the smoke-free environment, there was no significant change after exercise (2.1 \pm 1.9; $P > 0.05$), whereas in the smoking environment there was a significant increase (to

8.5 \pm 1.6, $P < 0.01$) after exercise. In survivors of myocardial infarction, the concentration prior to exercise was significantly lower in the smoking environment than in the smoke-free environment (0.6 \pm 0.2 versus 1.2 \pm 0.8, $P < 0.05$). In the smoke-free environment, there was no significant change in the concentration after exercise (1.3 \pm 0.6, $P > 0.05$), whereas in the smoking environment there was a significant increase (to 5.2 \pm 1.2, $P < 0.01$) after exercise. Although the two groups had different age distributions, there was no significant difference in the measurements between the survivors and the healthy volunteers, except for the concentration of expired carbon monoxide after exercise in the smoking environment (healthy 8.5 \pm 1.6 versus survivors 5.2 \pm 1.2, $P < 0.01$).

The results of concentration of carbon monoxide in the plasma are displayed in Table 5. In healthy volunteers there was no difference in the results prior to exercise between the smoking and smoke-free environments (1.4 \pm 0.2 versus 1.2 \pm 0.4%). In neither the smoking environment nor the smoke-free environment was there a significant change after exercise (1.7 \pm 0.4, $P > 0.05$ and 1.2 \pm 0.4, $P > 0.05$, respectively). In survivors of infarction there was no difference in the pre-exercise concentration between the smoking and smoke-free environments (1.2 \pm 0.16 versus 1.2 \pm

TABLE 4

Expired carbon monoxide (ppm): mean \pm SD; in the studied population.

Subjects	Smoking environment			Smoke-free environment		
	Pre-exercise	Post-exercise	t-test	Pre-exercise	Post-exercise	t-test
Healthy people	2.3 \pm 2.01	8.5 \pm 1.6	$P < 0.01$	2.3 \pm 2	2.1 \pm 1.9	$P > 0.05$
Survivors of infarction	0.6 \pm 0.2	5.2 \pm 1.2	$P < 0.01$	1.2 \pm 0.8	1.3 \pm 0.6	$P > 0.05$
t-test healthy/survivors	$P > 0.05$	$P < 0.01$		$P > 0.05$	$P > 0.05$	

TABLE 5

Plasma carbon monoxide (%): mean \pm SD; in the studied population.

Subjects	Smoking environment			Smoke-free environment		
	Pre-exercise	Post-exercise	t-test	Pre-exercise	Post-exercise	t-test
Healthy people	1.4 \pm 0.2	1.7 \pm 0.4	$P > 0.05$	1.2 \pm 0.4	1.2 \pm 0.4	$P > 0.05$
Survivors of infarction	1.2 \pm 0.16	2.3 \pm 0.4	$P < 0.001$	1.2 \pm 0.1	1.2 \pm 0.3	$P > 0.05$
t-test healthy/survivors	$P > 0.05$	$P < 0.05$		$P > 0.05$	$P > 0.05$	

0.1). In the smoke-free environment, there was no significant change in the plasma concentration after exercise (1.2 ± 0.3 , $P > 0.05$), whereas in the smoking environment there was a significant increase (to 2.3 ± 0.4 , $P < 0.01$) after exercise. Although the two groups had different age distributions, there was no significant difference in the plasma carbon monoxide measurements between the survivors and the healthy volunteers, except for the post-exercise plasma carbon monoxide in the smoking environment (healthy 1.7 ± 0.4 versus survivors 2.3 ± 0.4 , $P < 0.05$).

Discussion

For many people, exposure to environmental tobacco smoke is a potential hazard of daily life.

We planned this study since of many air pollutants, the components of cigarette smoke have an origin both indoors and outdoors [7], and can cause serious effects on the cardiovascular system [8].

Cigarette smoking can lead to catecholamine release which enhances platelet adhesiveness. Cigarette smoking and nicotine may also increase myocardial electrical instability, heart rate and systolic blood pressure exacerbating the atherosclerotic process. Carbon monoxide increases the blood's carboxyhemoglobin level because its affinity for hemoglobin is much greater than that of oxygen, diminishes oxygen transport capacity and damages directly myocardial mitochondria and endothelium [9].

Cardiac effects are the result of the degree of exposure to smoking and usually do not become apparent for days after exposure [10]. The acute response of the heart to passive smoking has not yet been carefully evaluated. Our data seem to show two different types of response, the one for the healthy subject and the other for the subject with previous myocardial infarction. However, some characteristics were similar.

A significant reduction of peak exercise power (33.4% in this study) has been seen in people with previous myocardial infarction who have undergone exercise stress testing in a smoking environment compared to their response in a smoke-

free environment ($P < 0.01$). Healthy people did not have impaired peak exercise power.

In a smoking environment, time to recovery of pre-exercise heart rate was prolonged in both groups. In our opinion that may be the consequence of decreased environmental oxygen availability. It is known indeed that the environment is fundamental for human homeostasis, and decreased environmental oxygen is potentially harmful for life.

Three main observations on expired carbon monoxide and plasma carbon monoxide can be made from this study. Firstly, pre-exercise and post-exercise measurements were similar or not statistically different ($P > 0.05$) for all people in a smoke-free environment. Secondly, in a smoking environment, post-exercise plasma carbon monoxide of survivors of infarction was statistically higher ($P < 0.05$) than that of healthy people. Thirdly, in the smoking environment post-exercise expired carbon monoxide was significantly lower ($P < 0.01$) in survivors of infarction if compared to healthy controls. Although there is a significant difference between the survivors and healthy controls as regards their post-exercise expired carbon monoxide and plasma carbon monoxide, this may not necessarily be due wholly or even partially to the previous myocardial infarction, as the two groups had different age distributions. Since the values of expired carbon monoxide and plasma carbon monoxide prior to exercise were similar ($P > 0.05$) in both groups, we believe the previous myocardial infarction combined with exercise stress testing in the smoking environment is a responsible factor of the aforesaid occurrence. Survivors of infarction often have cardiac failure, even if sometimes silent, as a probable consequence of impaired haemodynamics. Such pathology may affect the blood gas exchange as well as the ventilation/perfusion ratio. However, this hypothesis should be further investigated.

Acute exposure to passive smoke impairs the cardiac performance of both survivors of infarction and healthy volunteers. Survivors, who often have haemodynamic impairment, should avoid indoor spaces polluted by cigarette smoke. The fact that passive smoking also clearly affects the car-

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diac measurements made in the healthy volunteers has implications for public health and legislation.

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Sinzinger, H. and Kefalides, A., "Passive Smoking Severely Decreases Platelet Sensitivity to Antiaggregatory Prostaglandins," Letter, The Lancet II, pp. 392-393, August 14, 1982.

In this letter to the editor, the authors report an experiment involving exposure of both smokers and nonsmokers to ETS, examining effects on platelet sensitivity to the antiaggregatory effects of prostaglandins. The authors report that exposure to ETS reduced platelet sensitivity to prostaglandins, with this effect greater in nonsmokers than smokers. In view of the possible role of platelet actions in blood clotting and in atherosclerosis, it was suggested that these ETS-related changes in platelet activity may pose a risk to nonsmokers who are regularly exposed to ETS.

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PREPARATIONS USED IN THE COLLABORATIVE STUDY

Preparation	Subtype	HBeAg/ anti-HBe	Serum/ plasma	State
80/549*	ad	anti-HBe	Serum	Freeze dried
A	ad	HBeAg	Serum	Liquid
B	ad	anti-HBe	Plasma	Liquid
C	ay	HBeAg	Serum	Liquid
D	ay	anti-HBe	Serum	Liquid
E	ay	HBeAg	Serum	Liquid
F	ad	HBeAg	Serum	Liquid
G†	ad	anti-HBe	Serum	Freeze dried

*Proposed British Reference Preparation of Hepatitis B Surface Antigen.
†Coded duplicate of British Reference Preparation

Twelve laboratories contributed data from a total of 31 assays. All participants used solid phase radioimmunoassays—the 'AUSRIA II' commercial kit (Abbott) in six, a modification of the commercial kit in two,⁷ and the remaining four laboratories used their local method.

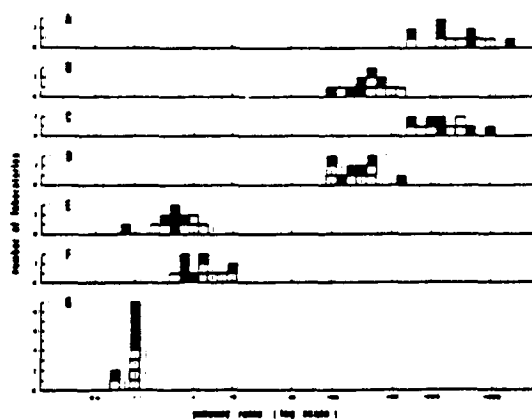
Assay data were analysed using the standard method of parallel line assays.⁸ Potencies of the samples were expressed relative to the proposed standard. For each sample, potency ratios from replicate assays of individual laboratories were combined by taking their geometric means. The frequency distributions of these values are shown in the figure.

No obvious difference were found between estimates obtained from laboratories using different forms of radioimmunoassay. There was reasonable agreement between the potency estimates obtained by the different laboratories. The potency estimates obtained for the coded duplicate of the standard (sample G) were remarkably close to unity. Furthermore, there was better agreement between laboratories for the potency of sample G than for the other samples. Nevertheless, the variation found between potency estimates of the individual coded preparations for the different laboratories were considered to be small in practical terms.

In 1982 the National Biological Standards Board authorised the establishment of the preparation coded 80/549 as the British Reference Preparation of Hepatitis B Surface Antigen (HsAg), with an assigned unitage of 100 units per ampoule.

The Hepatitis Advisory Group has recommended⁹ that all donations of blood destined to contribute to protein fractionation at

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9. Advisory Group on Testing for the Presence of Hepatitis-Associated Antigen and its Antibody. Third report, 1981.



Frequency distributions of potency estimates for samples A-G in terms of proposed reference preparation.

Each box denotes the mean potency obtained by one laboratory by radioimmunoassay: open boxes (Abbott commercial kit), hatched boxes (modification of Abbott kit), filled boxes (other methods).

N.H.S. fractionation centres should be tested by techniques that give a "positive" result for a concentration of 2 British units of HBeAg/ml. Subsequently a further study was carried out to estimate the detection limits, relative to the British Reference Preparation, of methods used by the participants. Preliminary results have shown that laboratories in the study detected the presence of hepatitis antigen at a concentration of 0.5 units/ml. In some laboratories as little as 0.125 units/ml could be routinely detected. Thus the assay methods used in the study should easily fulfil the recommendation of the Hepatitis Advisory Group.

We thank the following for participating in the study: Dr Elizabeth Boxall (Birmingham); Dr C. H. Cameron and Dr D. S. Dane (London); Dr R. J. Crawford (Carlisle); Dr R. Hopkins (Edinburgh); Dr R. S. Lane and Dr B. S. Combridge (Elstree); Dr Margaret Supran (London); Dr P. P. Mortimer (London); Dr E. G. Wheeler and Dr W. J. Jenkins (Brentwood); Prof. A. J. Zuckerman, Dr Hazel Smith, and Dr M. Bowerman (London); Dr R. J. Gerety (Bethesda, U.S.A.); Prof. R. Thomsen, Dr W. Gerlich, and Dr K. Legler (Göttingen, West Germany); and Dr P. J. Campbell, standards processing section, N.I.B.S.C., who organised the distribution of the ampoules.

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PASSIVE SMOKING SEVERELY DECREASES PLATELET SENSITIVITY TO ANTIAGGREGATORY PROSTAGLANDINS

SIR,—In the editorial (March 6, p. 548) and in the ensuing correspondence on passive smoking the risk of the development of atherosclerosis has not been mentioned. Unpublished studies (H. S. and O. Burghuber; and E. Walter) suggest that platelet function is severely affected in smokers, and there is some evidence that cigarette smoking might exert its action via diminished vascular prostacyclin (PGI₂) synthesis¹ and decreased sensitivity of platelets to antiaggregatory prostaglandins.² We have looked at the effects of passive smoking on platelet sensitivity.

We measured platelet sensitivity to the antiaggregatory prostaglandins (E₁, I₂, D₂) before, during, and after passive smoking in eight male and four female smokers aged 22-31 and in eight male and one female non-smokers aged 24-30. In a 18 m³ room thirty cigarettes of a strong brand ('Gitanes') were smoked by testers, to give a smoke concentration calculated to resemble that in discos, restaurants, and the like. The test subjects were exposed to the smoke for 15 min. Blood was sampled immediately before and at the end of the smoking period and 20 and 60 min afterwards from a cubital vein without occlusion, with 3.8% sodium citrate as anticoagulant.³ Platelet sensitivity as expressed as ID₅₀ (the amount of PG in ng/ml platelet-rich plasma necessary to halve the aggregation induced by 1 μmol/l ADP).

Passive smoking (table) reduced platelet sensitivity to the antiaggregatory PGs, being much more severe in non-smokers than in smokers. 20 min after passive smoking, platelet sensitivity started to return to basal values and this happened more quickly in non-smokers. However, the baseline values in smokers were significantly lower (p<0.01) than those in non-smokers.

A decrease in platelet sensitivity is the major determinant of haemostatic regulation⁴ and may thus be responsible for early changes preceding atherosclerosis.⁵ In combination with our

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PLATELET SENSITIVITY BEFORE AND AFTER PASSIVE SMOKING

PG	Before	End	20 min	60 min
Non-smokers				
I ₁	1.26±0.11	2.16±0.21*	1.76±0.21*	1.35±0.19
E ₁	18.7±3.1	32.5±4.2*	28.2±4.1*	24.7±2.8
D ₁	42.7±3.8	55.6±5.3	51.3±4.2	44.6±4.1
Smokers				
I ₁	1.75±0.26	2.08±0.19	2.06±0.18	1.93±0.23
E ₁	27.8±2.3	30.6±3.5	31.0±4.1	29.1±2.9
D ₁	44.9±4.1	48.6±4.8	49.8±3.7	45.2±3.8

Results in ng PG/ml protein rich plasma. Mean±SEM.

*p<0.01.

findings of decreased PGI₂ formation in umbilical arteries in babies born to mothers who smoked⁶ the severe changes we found after passive smoking, especially in non-smokers, point to an important risk in non-smokers exposed to cigarette smoke for a long time. Although not much is known about the long-term influence of passive smoking on the risk for development of atherosclerosis, our data do indicate that passive cigarette smoking, besides being an important social issue, may be a health problem too.

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EARLY TREATMENT OF OESOPHAGEAL VARICES

SIR,—While we agree with Freeman and colleagues (July 10, p. 66) that vasopressin or its analogues may have a place in the management of acute variceal bleeding, we believe its role is at best subsidiary. Since the patients most at risk are those who rebleed early, the aim of management in variceal bleeding should be to prevent rebleeding as much as to control the presenting haemorrhage. To this end we have developed a practice of managing variceal bleeding which provides results equally as good as those obtained with glypressin by Freeman et al. and which also serves as a basis for long-term management.

If bleeding is active, a Linton tube¹ is inflated in the gastric fundus and maintained on traction. When resuscitation is effected the varices are immediately injected with sclerosant with the tube in situ. As there is no oesophageal balloon on this tube, injection is not technically difficult and there is the advantage that a bloodless field is obtained. Furthermore, it seems likely that pressure on the gastric varices aids sclerosis by preventing retrograde flow of sclerosant. If there is no active bleeding at the time of endoscopy the varices are injected without the tube, which can be passed later if bleeding becomes a difficulty. Sclerosis is continued fortnightly until variceal obliteration is complete.

Since adopting this policy 18 months ago we have treated sixteen patients with acute variceal bleeding. One died immediately on admission to hospital before endoscopy could be carried out. Of the remainder, eight had sclerotherapy with the Linton tube in situ and seven had it without the tube. Of these patients, one rebled three times before dying of liver failure due to hepatic angiosarcoma; the other fourteen remain well, although two rebled before their varices were obliterated.

While glypressin might be of value in variceal bleeding when endoscopic sclerotherapy is unavailable, we believe that our simple policy may be of greater value in most general hospitals.

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ICOSAPENTAENOIC ACID AND ISCHAEMIC HEART DISEASE

SIR,—Dr Jones and Dr Davies (July 24, p. 221) discuss the decrease in circulating platelets which various workers have found to be produced by fish oils. But they state that Hay and colleagues¹ used "a similar fish oil and EPA supplement" to that used by Thorngren and Gustafson.² There was a crucial difference. Hay et al. used "Maxepa" (Marflet Refining Company, a subsidiary of Imperial Foods), which is a refined deodorised blend of marine body oils with added antioxidants; it contains about 20% of fatty acids as rumnodonic (C20:5n-3 or "EPA"), about 19% as clupanodonic (C22:6n-3) and less than 1% as ceroleic (C22:1n-11). The first two are essential fatty acids and the third is toxic, at least to lower animals, being an isomer of erucic acid (C22:1n-9) found in certain rapeseed oils, which cannot be oxidised with ease by muscle mitochondria unless adaptation has occurred and therefore causes myocardial fibrosis with sudden death. Thorngren's volunteers, however, changed their usual Swedish diet for eleven weeks to include "a predominance of fish, mainly mackerel and salmon". These fish have ceroleic acid as a predominant fatty acid, analyses (in % of total acids) by Dr Mary Gale in our Institute being:

Oil	C20:5	C22:6	C22:1
Mackerel (<i>Scomber scombrus</i>)	12.1	11.4	9.0
Salmon (<i>Salmo salar</i>)	10.2	11.4	11.3

The relevance of C22:1 fatty acids is that they probably decrease the number of circulating platelets. McDonald and colleagues³ fed seven healthy males for 22 days with rapeseed oil containing 39% erucic acid (which supplied 38% total dietary energy); in five of them there was a marked fall in platelet count which returned to normal when their customary diet was resumed. On a traditional Eskimo diet for 100 days (only seal, fish, and water) my platelet count decreased from 226 000/ μ l to 52 000/ μ l, and platelets changed morphologically to giant forms; this diet was very high in C20:5, C22:6, and C22:1. The first of these tended to displace arachidonic acid (C20:4n-6) in, for instance, the different phospholipids of platelets⁴ and ceroleic acid appeared in these as well as in lipoproteins, erythrocyte membranes, adipose tissue, and skeletal muscle. But the dramatic increase in bleeding time was probably caused partly by the alteration in the structure and therefore fluidity of the platelet membranes and not only by the observed alterations in prostanooids; the former may also have contributed to the decrease in platelet count since Hay et al.¹ observed a decrease on a diet containing negligible ceroleic acid.

The references in Jones and Davies' letter raise an important question of nomenclature. They twice refer to rumnodonic acid (C20:5n-3) as "eicosapentaenoic". This word contains three errors—one academic, one careless (the second "o" should be "a"), and one fundamental. The I.U.P.A.C.-I.U.B. Commission on Biochemical Nomenclature has decreed⁵ in its wisdom (or folly) that the Greek *eikosi* (or the common Epic dialect form *ekikosi*) must be anglicised as "icosa," thereby dropping one or two epsilon's: so "EPA" must be "IPA". To be on the right side, Professor Crawford and colleagues⁶ from the Royal College of Surgeons in a current paper use both spellings in different places. But trivial names for fatty acids are useful; let us continue to call C20:5n-3 rumnodonic acid and C22:6n-3 clupanodonic acid.

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Burghuber, O.C., Punzengruber, Ch., Sinzinger, H., Haber, P. and Silberbauer, K., "Platelet Sensitivity to Prostacyclin in Smokers and Non-smokers," Chest 90(1): 34-38, 1986.

This study examined the responses of platelets to prostacyclin in both smokers and nonsmokers, both following "active" smoking and following ETS exposure. Prostacyclin is an antiaggregatory agent. Thus, a decrease in responsiveness to prostacyclin would be reflected in increased platelet aggregation, which has been suggested as a mechanism underlying atherosclerosis or thrombus formation.

The authors reported a chronic effect of smoking reflected in a lesser sensitivity of smokers' platelets to the antiaggregatory effects of prostacyclin than the platelets of nonsmokers. Furthermore, both "active" smoking and ETS exposure were reported to have acute effects on decreasing the responsiveness of platelets to prostacyclin, although this effect was observed only in nonsmokers.

These results were characterized as supporting a proaggregatory effect (via decreased platelet sensitivity to an antiaggregatory agent) of both smoking and ETS exposure, thus providing a mechanism for how tobacco smoke might be involved in clinical thromboembolic diseases.

2023512226

Platelet Sensitivity to Prostacyclin in Smokers and Non-smokers*

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Platelet activating effect of cigarette smoking appears to be important in the development of atherosclerosis. We previously demonstrated a reduced sensitivity of platelets to exogenous prostacyclin (PGI₂) *in vitro* from patients with proven atherosclerotic disease, indicating a possible role of altered platelet function in the development of atherosclerosis. We now hypothesize that cigarette smoking might be an important cause of altered platelet sensitivity to PGI₂ observed in patients with atherosclerosis. To test this hypothesis, the response of platelets to exogenous PGI₂ was tested in chronic smokers and non-smokers, prior to and

after smoking two cigarettes (active smoking) and prior to and after exposure to a tobacco smoke-contaminated atmosphere (passive smoking). This study indicates that platelets of chronic smokers are less sensitive to exogenous PGI₂ than platelets of non-smokers. In addition, active as well as passive smoking decreases platelet sensitivity to PGI₂ in non-smokers, whereas chronic smokers exhibit no further decline. We conclude that decreased platelet sensitivity to PGI₂ might be an important contributing factor to the altered platelet function observed in patients with atherosclerosis.

Smoking has been incriminated as a pathogenetic factor in cardiovascular disease.^{1,2} Tobacco smoking is associated with an increased risk of myocardial infarction,³ sudden death and arterial thrombosis occur more frequently in cigarette smokers.^{4,5} Because blood platelets appear to play a central role in the initiation of arterial thrombosis, the difference in aggregation behavior in platelets from smokers and non-smokers seems to be important. The influence of nicotine and/or other cigarette constituents on platelet function has been investigated in several *in vivo* and *in vitro* studies. From these studies it is known that smoking induces enhancement of platelet function.⁶ Evidence supporting this idea includes an association of smoking with increased ADP-induced platelet aggregation in platelet-rich plasma,⁷ an enhanced tendency of platelets to aggregate in blood,^{8,9} a shortening of platelet survival¹⁰ and increased thromboxane synthesis.^{11,12} In addition there is some evidence that smoking might exert its action by reducing vascular prostacyclin (PGI₂) synthesis.¹³ Since we have previously demonstrated reduced platelet sensitivity to exogenous PGI₂ *in vitro* in patients with atherosclerosis,¹⁴ we wondered whether cigarette smoking might decrease platelet sensitivity to PGI₂. Because of recent observations¹⁵⁻¹⁸ that passive smoking increases the incidence of various diseases primarily associated with active smoking, we also wondered whether even passive smoking could influence platelet sensitivity to PGI₂. If platelet sensitivity to PGI₂ were suppressed by active or passive

smoking, then we could consider it an additional important mechanism of arterial thrombosis.

MATERIAL AND METHODS

Active Smoking

The subjects of this study were 14 healthy male volunteers whose ages ranged from 28 to 36 years. Seven were non-smokers and seven were moderate-to-heavy smokers (at least one pack a day for at least ten years). Standard commercial brands containing 1.5 mg nicotine and 25 mg tar per gram of cigarette were used. The smokers refrained from smoking for at least four hours prior to the test procedures, and no medication was allowed for two weeks prior to the studies. A 19 gauge plastic cannula was inserted into the antecubital vein 15 min prior to baseline measurements to avoid repeated venous punctures. Then the patients were told to smoke two cigarettes, one after the other, within 10 min. Immediately before and 15 min after smoking two cigarettes, blood pressure, pulse rate, and ventilatory function tests were performed and blood was drawn. Blood pressure was measured with the Korotkoff method by the same observer. Ventilatory function was assessed by spirometry using a Fleisch pneumotachograph attached to an electronic device (Siregnost FD 10, Siemens Elema, 19) and recorded on an x-y recorder (Hewlett-Packard). Vital capacity (VC, L) was determined by a slow inspiratory effort.

This was followed by three attempts of FEV₁ maneuvers (FEV₁, L). After completion of these procedures, forced expiratory flow volume curves were obtained. Forced expiratory flows at the moment when 50 percent of the vital capacity had been expelled (FEF₅₀, L/sec) and when 75 percent had been expelled (FEF₇₅, L/sec) were read directly from the flow volume curves. The best of three attempts was used for calculation.

Blood withdrawal was performed from the previously inserted plastic cannula. Nine volumes of blood were mixed with one volume of 3.8 percent trisodium citrate solution to obtain citrated blood. After centrifugation at 150 g for 5 min, platelet-rich plasma (PRP) was obtained. PRP was then removed and platelet-poor plasma (PPP) produced by further centrifugation of 1500 g for 15 min. PRP was adjusted with PPP to give a platelet count of approximately $250 \times 10^9/\mu\text{L}$. ADP (in a rather high concentration of 1 mmol/L) was used to cause irreversible platelet aggregation measured in a Born-

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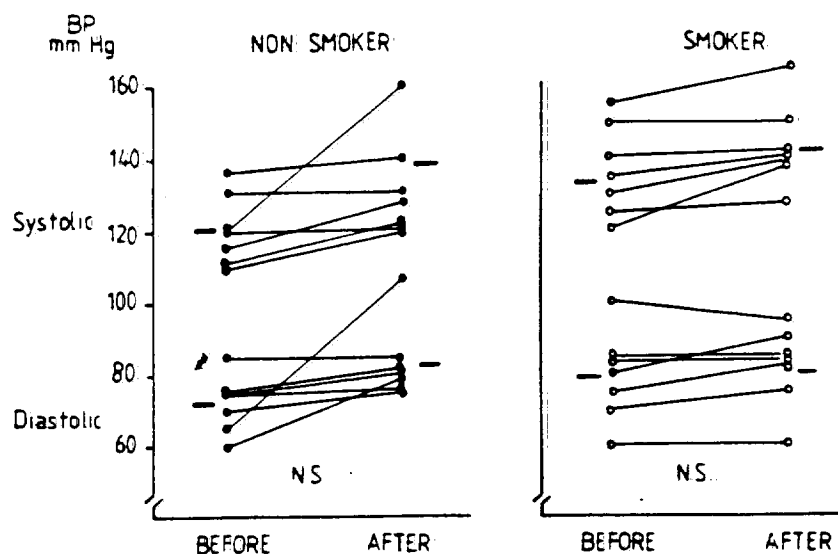


FIGURE 1. Individual data points and means of systolic and diastolic blood pressure (BP, mmHg) before and after smoking 2 cigarettes in smokers and non-smokers.

type aggregometer. On all occasions, second phase of ADP-induced platelet aggregation was seen. The maximal extent of platelet aggregation (ΔT_{max}) was calculated assuming that PPP was 100 percent and PRP was 0 percent aggregation. In addition, ADP-induced platelet aggregation was inhibited by increasing concentrations of PGI_2 (1.2.3 ng/ml) being added 60 sec prior to ADP. From this the sensitivity index of PGI_2 (SI_{PGI_2}) was calculated ($SI_{PGI_2} = 1/ID_{50}$, ID_{50} = the concentration of PGI_2 necessary to inhibit ADP-induced platelet aggregation to 50 percent).

Passive Smoking

Another 22 healthy male volunteers, 13 smokers and nine non-smokers, whose ages ranged from 25 to 40 years, were exposed to cigarette smoke. Smokers refrained from active smoking for at least four hours before studied.

Volunteers were kept for 20 min in an 18 m² room in which testers smoked 30 heavy brand cigarettes just prior to the exposure period. This concentration was calculated to be that occurring in discos, restaurants etc. Again, blood was drawn before and 15 min after the passive smoking period and aggregation studies were performed as previously described.

Statistical Analysis

Paired and unpaired Student's *t*-tests were used to compare results

within and between groups respectively. Differences were considered significant when $p < 0.05$.

RESULTS

Active Smoking

Prior to smoking two cigarettes, neither smokers nor non-smokers exhibited any difference in either systolic or diastolic blood pressure (Fig 1) or in heart rate (Fig 2). After smoking two cigarettes, blood pressure remained unchanged (Fig 1), whereas a significant increase in heart rate could be observed in both groups (Fig 2). There was no difference in VC and FEV₁ prior to or after smoking between smokers and non-smokers (Table 1). However, smokers had lower forced expiratory flow rates compared to non-smokers, before as well as after smoking two cigarettes (Table 1). Smoking two cigarettes did not alter any ventilatory parameters studied in either group.

Prior to smoking two cigarettes, the aggregation of platelets in response to ADP was the same in smokers

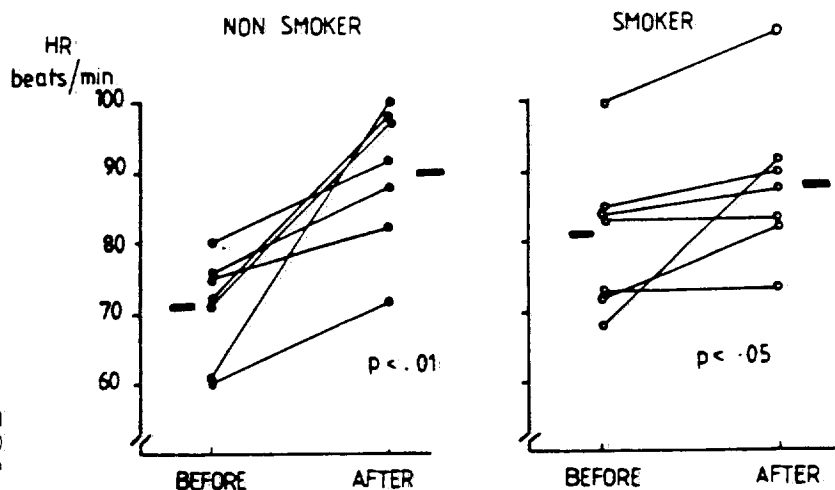


FIGURE 2. Individual data points and means of heart rate (HR, beats/minute) before and after smoking 2 cigarettes in smokers and non-smokers.

Table 1—Individual Lung Function Parameters before and after Smoking Two Cigarettes in Non-smokers and Smokers

	VC (L)		FEV ₁ (L)		FEF ₂₅₋₇₅ (L/sec)		FEF ₅₀₋₇₅ (L/sec)	
	Before	After	Before	After	Before	After	Before	After
Non-smokers								
1	6.5	6.1	4.3	4.6	4.3	5.4	2.2	2.8
2	7.8	7.6	5.8	6.2	11.4	9.4	3.7	5.3
3	6.4	6.5	5.6	5.8	5.6	5.8	2.9	3.3
4	5.6	5.8	3.7	4.6	5.1	4.8	2.6	2.4
5	3.5	3.6	2.8	2.7	4.3	3.5	2.4	1.4
6	4.5	4.9	4.3	3.7	5.9	5.2	4.5	4.1
7	5.6	4.8	4.0	3.9	5.1	4.1	2.1	2.1
mean ± SEM	5.7 ± 0.5	5.6 ± 0.5	4.3 ± 0.4	4.5 ± 0.5	6.0 ± 0.9	5.5 ± 0.7	2.9 ± 0.3	3.1 ± 0.5
Smokers								
1	5.3	5.5	4.1	4.6	6.2	7.3	3.7	3.9
2	6.4	6.3	5.1	4.5	5.2	5.2	2.4	2.2
3	4.6	4.7	3.2	3.5	3.9	3.1	2.7	1.4
4	6.0	6.5	4.5	4.5	5.0	4.8	2.2	2.7
5	5.8	5.7	4.2	4.2	4.7	4.5	2.6	2.1
6	3.9	4.46	2.9	2.9	3.0	2.6	1.1	1.2
7	4.6	4.7	3.5	3.2	3.5	3.1	1.6	1.0
mean ± SEM	5.3 ± 0.4	5.4 ± 0.3	3.9 ± 0.3	3.9 ± 0.3	4.5 ± 0.4*	4.3 ± 0.6*	2.3 ± 0.3*	2.0 ± 0.4†

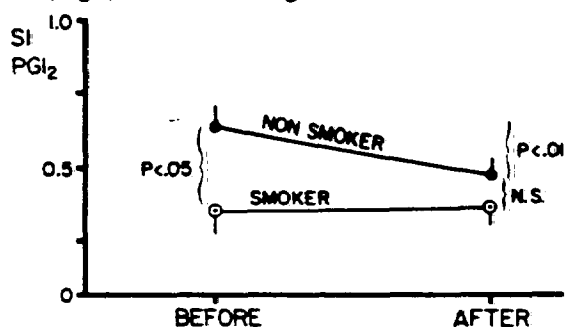
*p < 0.1

†p < 0.05, smokers vs non-smokers

and non-smokers (48 ± 4 percent in smokers vs 44 ± 4 percent in non-smokers). However, platelet sensitivity to PGI₂, expressed as sensitivity index to PGI₂, was significantly lower in smokers compared to non-smokers (Fig 3). After smoking two cigarettes, ADP-induced platelet aggregation did not change in either group (49 ± 2 percent in smokers vs 50 ± 2 percent in non-smokers). In contrast, the sensitivity index to PGI₂ significantly decreased in non-smokers, almost reaching baseline-level for smokers (Fig 3). In smokers, however, no further decrease in platelet sensitivity to PGI₂ could be observed. Thus, after smoking two cigarettes, no further statistically significant difference between smokers and non-smokers could be found.

Passive Smoking

Sensitivity index to PGI₂ again was significantly lower in the smoker group as compared to non-smokers (Fig 4). Passive smoking in non-smokers induced a

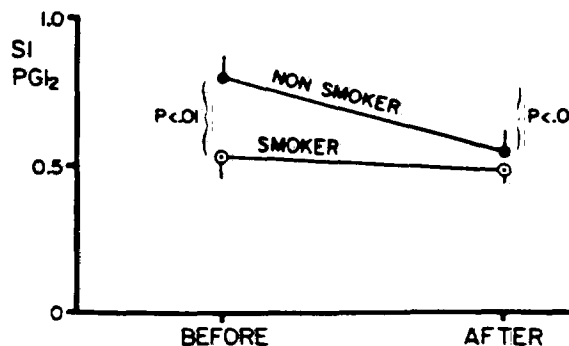
FIGURE 3. Sensitivity index of PGI₂ (SI_{PGI₂}) before and after smoking 2 cigarettes in smokers and non-smokers.

significant decrease in platelet sensitivity to PGI₂, whereas in smokers no further decrease could be demonstrated.

DISCUSSION

The main finding of this study is that smokers' platelets are less sensitive to the anti-aggregatory action of exogenous PGI₂ compared to platelets of non-smokers. Further, our results show that only in non-smokers does acute inhalation of tobacco smoke decrease platelet sensitivity to PGI₂ *in vitro*. Finally, a decrease in platelet sensitivity to PGI₂ was observed in non-smokers after active as well as after passive smoking.

It is well-established that platelet sensitivity to PGI₂ is a reliable and sensitive test to examine platelet function.^{20,21} In our experiments, there were two lines of evidence for the reliability of this procedure. First, platelet sensitivity to PGI₂ was reproducible in two dif-

FIGURE 4. Sensitivity index of PGI₂ (SI_{PGI₂}) before and after passive smoking in smokers and non-smokers.

ferent populations (eg, in 14 volunteers smoking actively and in 21 volunteers smoking passively). Second, platelet sensitivity to PGI_2 was sensitive in distinguishing between the platelet function of smokers and non-smokers. Thus, it appears that this procedure is of additional value in examining platelet function in various circumstances. However, as with other platelet function tests, we do not know if this *in vitro* procedure accurately reflects platelet function *in vivo*.

We have used a rather high concentration of ADP, previously shown to be optimal for measurements of platelet sensitivity to PGI_2 .²⁰ Therefore, our results of ADP-induced platelet aggregation cannot be compared with a previous study⁶ using different, lower concentrations of ADP. This study showed a significant increase of ADP-induced platelet aggregation after smoking. Nevertheless, even with the high ADP-concentration used in this study, there was a tendency towards an increase in ADP-induced platelet aggregation after smoking two cigarettes in the non-smoker group.

The influence of cigarette smoking on platelet function has been investigated in several *in vitro* and *in vivo* studies.⁷⁻¹² Although the precise effect is not clear, in most studies potentiation of platelet aggregation has been observed. Our findings of a diminished platelet sensitivity to an anti-aggregatory substance in smokers fits into the overall idea of a proaggregatory effect of cigarette smoking. Chronic smoking can desensitize blood platelets to PGI_2 ; such platelets would hypothetically be more ready to aggregate and participate in plug formation, leading to arterial thrombosis. Our results are thus in agreement with the well-known clinical finding of the increased incidence of thromboembolic diseases in smokers.²¹ Since causes other than smoking could conceivably have led to a decrease in platelet sensitivity to PGI_2 observed in our smokers, we investigated whether smoking two cigarettes would acutely influence platelet sensitivity to PGI_2 . A significant decrease in platelet sensitivity to PGI_2 in non-smokers indicated that cigarette smoking is responsible for the decreased platelet sensitivity to PGI_2 in smokers.

The fact that acute smoking did not alter platelet sensitivity to PGI_2 in chronic smokers remains to be clarified. One explanation is that smoking two cigarettes exhibits a much lower emotional stress in smokers than in non-smokers. Since platelet aggregation has been shown to vary with emotional stress,²² this could have led to a different platelet behavior after acute smoking. We did not measure plasma epinephrine concentrations parallel to platelet function in this study. However, if one compares blood pressure and heart rate before and after smoking two cigarettes in smokers and non-smokers, one will find: a) no statistical significant changes in blood pressure, and b) a

similar, marked increase in heart rate in both groups. Despite not being statistically significant, there was an obvious increase in systolic and diastolic blood pressure after smoking two cigarettes in the non-smoking group (Fig 1). This increase could have reached statistical significance if more patients had been studied. Nevertheless, it seems unlikely that different adrenergic stimuli were responsible for the difference in platelet behavior after acute smoking.

An alternative explanation is that acute smoking influences lung function parameters differently in smokers and non-smokers, which could cause differences in platelet function. Since no significant change in lung function could be demonstrated in either group after smoking two cigarettes, we strongly feel that differences in lung function cannot account for the different behavior in platelet sensitivity to PGI_2 after acute smoking. It is interesting to note, however, that smokers revealed lower forced expiratory flow rates at 50 and 25 percent of vital capacity compared to non-smokers (table 1). These findings confirm previous studies^{23,24} indicating some degree of small airways disease in smokers. Finally, platelets of chronic smokers may already be desensitized to an extent where no further decrease is possible, but this alternative was not clarified.

In recent years the possible consequences to the health of non-smokers exposed to cigarette smoke (passive smoking) have been examined.^{15,25} It has been shown that passive smoking could lead to deterioration of lung function in adults²⁶ and children.^{27,28} Further, the effect of passive smoking on the development of lung cancer was studied epidemiologically in Japan,¹⁷ indicating the possible importance of passive smoking as one of the causal factors of lung cancer. To our knowledge, there is no evidence published so far indicating a higher risk of developing arterial thrombosis in passive smokers.

In the present study of healthy male non-smokers, we found a significant decrease in platelet sensitivity to PGI_2 after acute passive exposure to tobacco smoke. This finding at least suggests that platelets of non-smokers passively exposed to tobacco smoke might also exhibit a higher tendency to aggregate. Further investigation is needed to elucidate whether this finding is important with respect to a possible increased incidence of thromboembolic disease among non-smokers passively exposed to cigarette smoke.

In any event, the present study has suggested that active and passive tobacco smoking is primarily responsible for a decrease in platelet sensitivity to PGI_2 *in vitro*. Although the results obtained *in vitro* cannot be directly extrapolated to *in vivo* situations, they may extend our understanding of the mechanisms by which smoking increases the risk of embolic disease.

Sinzinger, H. and Virgolini, I., "Are Passive Smokers at Greater Risk of Thrombosis?" Wiener Klinische Wochenschrift 20: 694-698, 1989.

This is a German language article with an English abstract. The abstract reports that ETS exposure has similar proaggregatory effects on platelets as does cigarette smoking. These results are suggested as providing a mechanism whereby ETS exposure might contribute to the incidence of atherosclerosis and thrombosis.

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Originalarbeiten

Besitzen Passivraucher ein erhöhtes Thrombosensisiko?

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7611a Are passive smokers at greater risk of thrombosis?

Summary. In contrast to the proven association between active smoking and vascular injury, as well as hemostatic imbalance, such a relation is not yet proven for passive smoking. Vascular damage induced by smoking, however, can be seen in the materno-fetal circulation of smoking mothers, being much more pronounced in the umbilical system than in fetal vessels. These lesions show fast recovery after birth. In non-smokers acute exposure to passive smoke induces a short-lasting activation of platelet function and the prostaglandin system, followed by a quick recovery. Chronic exposure of non-smokers to passive smoke, however, results in changes of these parameters comparable to those seen in smokers, characterized by an activation of platelet function and a decrease in platelet sensitivity to the antiaggregatory prostaglandin I_2 . These results suggest that in non-smokers with atherogenic risk factors passive smoking may contribute to the incidence of atherosclerosis, as well as acute complications (thrombosis).

Key words: Cigarette smoking, non-smoker, smoker, platelet function, prostaglandin system.

Zusammenfassung. Im Gegensatz zu dem heute als sicher geltenden Zusammenhang zwischen aktivem Zigarettenrauchen und Schädigungen am Gefäßsystem sowie der Hämostase

ist dieser hinsichtlich passives Inhalieren von Zigarettenrauch nicht gesichert. Einzig im materno-fetalen Kreislauf kann bei rauchenden Müttern eine Gefäßschädigung eindeutig belegt werden. Sie ist am Umbilikalsystem stärker ausgeprägt als im Gefäßsystem des Kindes und zeigt eine rasche Rückbildung nach der Geburt. Beim Nichtraucher führt eine akute passive Rauchexposition zu kurzdauernden und sich rasch normalisierenden Veränderungen der Plättchenfunktion und des Prostaglandinsystems. Eine chronische passive Rauchexposition führt hingegen beim Nichtraucher zu einer Annäherung dieser Parameter an eine dem Raucher ähnliche Situation, die durch eine Aktivierung der Plättchen und eine verminderte Plättchensensitivität gegenüber antiaggregatorischem Prostaglandin I_2 gekennzeichnet ist. Diese Befunde legen die Vermutung nahe, daß bei Vorhandensein von atherogenen Risikofaktoren das Passivrauchen zur Atheroskleroseinzidenz bzw. akuten Komplikationen (Thrombose) bei Nichtrauchern beitragen könnte.

Schlüsselwörter: Zigarettenrauch, Nichtraucher, Raucher, Plättchenfunktion, Prostaglandinsystem.

Einleitung

Das natürlich vorkommende Alkaloid der *Nicotiana tabacum*, Nikotin, verfügt auf Grund seiner ver-

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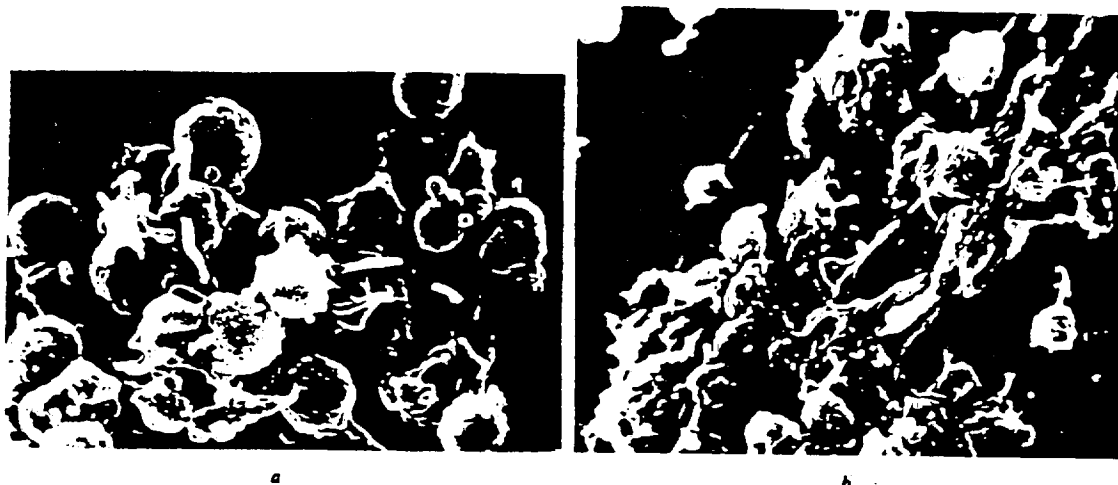


Abb. 1. Rasterelektronenoptische Darstellung menschlicher Blutplättchen: (a) „ruhende“ (vor) und (b) aktivierte Plättchen von einem Nichtraucher (nach Passivrauchen) unter identischen Aufarbeitungsbedingungen (Gesamtvergrößerung 6800mal)

gleichbaren Strukturmerkmale mit verschiedenen Zykllooxygenaseinhibitoren [10] wie Aspirin [24] bzw. Indomethacin [2] über eine Hemmwirkung auf das Prostaglandinsystem. „Rauch“ (Nikotin/Kohlenmonoxyd) hemmt die vaskuläre Zykllooxygenase und damit die Bildung von antiaggregatorisch wirksamen Prostaglandin I_2 (PGI_2) [13]. Nikotin bewirkt einen Formwandel der Plättchen (Abb. 1). Die damit verbundene Aktivierung spiegelt sich in einer vermehrten Sekretion von proaggregatorisch wirksamem Thromboxan A_2 (TXA_2) [15, 17], plättchenspezifischer Proteine [20] und auch einer gesteigerten Aggregabilität der Plättchen, die von der Nikotinkonzentration abhängig ist [5], wider.

Die Interaktion der Plättchen mit der Gefäßwand wird durch das TXA_2 - PGI_2 -System geregelt [19]. Das vorwiegend von den Endothelzellen produzierte PGI_2 verhindert die Anlagerung der Plättchen an eine mit intaktem Endothel ausgekleidete Gefäßwand [14]. Diese Befunde lassen den Schluß zu, daß Nikotin die Plättchen aktiviert und daher atherogen wirkt. Diese vorwiegend tierexperimentell erhobenen Befunde konnten an aktiv rauchenden Personen bestätigt werden [3, 6, 18, 23].

Hingegen existieren noch keine endgültigen Aussagen über den Einfluß von Passivrauchen auf die genannten Parameter bei Nichtrauchern.

Wir wollen die möglichen bzw. gesicherten Auswirkungen von passiv inhaliertem Zigarettenrauch, unter akuter und chronischer Exposition, auf die Gefäßwand, sowie Plättchenfunktion und das Prostaglandinsystem bei Rauchern bzw. Nichtrauchern vergleichen.

Ergebnisse

Gefäßwand

Eine Reihe von Hinweisen macht einen direkten Zusammenhang zwischen mütterlichem Rauchkonsum und perinatalen Komplikationen wahrscheinlich. Nikotin und/oder Rauchinhaltsstoffe beeinflussen die fetale

Herzaktion [16] und Durchblutung [12]. Intrauterin sind sowohl die Durchgängigkeit des Ductus arteriosus als auch der Gefäßtonus der Umbilikalgefäße Prostaglandin-abhängig. Die PGI_2 -Synthesekapazität [7] ist bei rauchenden Müttern signifikant vermindert [8, 9]. Zwischen erniedrigter Plazentadurchblutung und verminderter PGI_2 -Synthese der Umbilikalgefäße wurde darüber hinaus eine signifikante Korrelation beschrieben [1]. Auch eine verminderte Oberflächenauskleidung durch Endothelzellen sowie abschilfernde Zellen (Abb. 2) und andere morphologische Kriterien einer Gefäßschädigung lassen sich nachweisen [4]. Die großen Arterien zeigen wesentlich stärkere Frñhschädigungen, wie eine Verdickung der Gefäßintima, Endothelzelldesquamation, „fatty dots“ und „fatty streaks“.

In-vitro-Studien über die Auswirkung von Nikotin auf diverse Gefäßzellkulturen liefern allerdings nur indirekte Anhaltspunkte. Sie sind für eine Prüfung des Einflusses von Passivrauchern bzw. eine In-vivo-Aussage nicht brauchbar.

Thrombozytenfunktion und Prostaglandinsystem

In einem 18 m³ großen Raum (22°C, 60% relative Luftfeuchtigkeit) wurden 30 Zigaretten der Marke „Gitanes“ (1,5 mg Nikotingehalt, 25 mg Teerinhaltsstoffe) geraucht. Aktiv rauchende 6 F., 2 M., 22 bis 30 Jahre) und nicht rauchende freiwillige Testpersonen (6 F., 2 M., 24 bis 30 Jahre) wurden diesem Rauch passiv für 60 Minuten einmalig bzw. wiederholt (10mal in Serie, täglich einmal) exponiert. Die Plättchenfunktion (β -Thromboglobulin (β -TG), RIA, Amersham, England; Plättchenfaktor 4 (PF4), RIA, Abbott USA; Plättchenmigration, ADP-(1 μ M)-induzierte Aggregation, Plättchenadhäsion in Glasperlensäulen, zirkulierende Mikroaggregate nach Wu [25], zirkulierende Endothelzellen nach Hladovec [11] und das Prostaglandinsystem (Plasma- TXB_2 , Malondialdehyd (MDA), HHT und Plättchensensitivität gegenüber PGI_2) wurden untersucht. Blutabnahmen aus einer ungestauten Kubitalvene

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Abb. 2: Elektronenmikroskopische Aufnahme (Gesamtvergrößerung 14.640mal) einer geschädigten Gefäßoberfläche (Nabelschnurarterie: Mutter aktive Raucherin, bis 30 Zigaretten/Tag) mit freiliegenden subendothelialen Strukturen und einer sich abschilfernden Endothelzelle

erfolgten vor, unmittelbar nach sowie 20 und 60 Minuten sowie 6 Stunden nach der Rauchexposition.

Akute Wirkung von Zigarettenrauch

Abgesehen von den Plättchenproteinen β -TG und PF4 zeigen alle gemessenen Parameter eine signifikante Änderung um etwa ein Drittel, die bei Nichtraucherinnen nach 6 Stunden nicht mehr nachweisbar ist (Tabelle 1). Ebenso zeigen Plasma-TXB₂ und MDA unter Akutexposition eine Aktivierung, die nach 6 Stunden nicht mehr vorhanden ist (Tabelle 2). Plättchen zeigen nach Zigarettenrauchen auch morphologisch eine deutliche Aktivierung (Abb. 2). Bei Nichtrauchern fällt schon nach einer relativ kurzen Exposition von nur 15 Minuten gegenüber Passivrauchen eine signifikante ($p < 0,01$) erniedrigte Sensitivität gegenüber PGI₂ im Vergleich zum Ausgangswert auf. Im Gegensatz zur Rauchergruppe, bei der schon vor der standardisierten Rauchexposition ein pathologisch erniedrigter Ausgangswert gefunden wird, ist bei den Nichtrauchern der Einfluß des Passivrauchens auf die Plättchensensitivität wesentlich stärker ausgeprägt. Die Ausgangswerte werden allerdings bei den Nichtrauchern schneller wieder erreicht.

Tabelle 1. Plättchenfunktionsparameter von Nichtrauchern (erste Zeile) und Rauchern (zweite Zeile) bei einmaligem bzw. wiederholtem Passivrauchen

	einmalig		wiederholt		
	akut	6 Std.	vor	akut	6 Std.
Adhäsion	31 ± 7 14 ± 5*	0 ± 4 2 ± 3	17 ± 6 0 ± 5*	36 ± 8 15 ± 4*	28 ± 3 1 ± 4*
Aggregation	18 ± 8 7 ± 5*	4 ± 3 -2 ± 4	10 ± 4 1 ± 4*	24 ± 6 6 ± 3*	17 ± 4 2 ± 3*
Migration	26 ± 5 10 ± 6*	1 ± 5 -1 ± 2	12 ± 3 -1 ± 2*	29 ± 7 8 ± 5*	19 ± 5 4 ± 4*
β -TG	11 ± 3 7 ± 4	2 ± 2 0 ± 3	10 ± 4 -1 ± 2*	16 ± 4 8 ± 3*	12 ± 4 2 ± 3*
PF4	13 ± 5 6 ± 2*	0 ± 3 2 ± 4	8 ± 3 1 ± 3*	18 ± 3 6 ± 3*	14 ± 4 3 ± 3*
zirkulierende Aggregate	33 ± 6 19 ± 7*	2 ± 4 5 ± 3	19 ± 7 2 ± 4*	43 ± 8 17 ± 6*	30 ± 4 4 ± 2*
Endothelzellen	36 ± 7 20 ± 6*	2 ± 3 6 ± 4	18 ± 5 4 ± 3*	44 ± 8 19 ± 3*	26 ± 4 -2 ± 5*

n = 8. *%-Änderung: $\bar{x} \pm$ SD. - $p < 0,01$. Student-t-Test zwischen beiden Gruppen.

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Tabelle 2. Prostaglandinsystem von Nichtrauchern (erste Zeile) und Rauchern (zweite Zeile) bei einmaligem bzw. wiederholtem Passivrauchen

	einmalig		wiederholt		
	akut	6 Std.	vor	akut	6 Std.
TXB ₂	30 ± 6 17 ± 5*	2 ± 3 -2 ± 4	14 ± 5 -1 ± 5*	36 ± 4 16 ± 5*	30 ± 6 5 ± 4*
MDA	22 ± 4 11 ± 4*	3 ± 4 0 ± 3	10 ± 4 2 ± 4*	29 ± 5 10 ± 6*	22 ± 5 3 ± 3*
HHT	19 ± 3 13 ± 4*	2 ± 3 -1 ± 3	8 ± 4 0 ± 3*	24 ± 4 15 ± 4*	19 ± 4 4 ± 2*
IC-50/PGI ₂	34 ± 5 17 ± 5*	1 ± 3 1 ± 3	15 ± 5 0 ± 3*	40 ± 3 18 ± 7*	31 ± 5 5 ± 6*

n = 8; % Änderung; $\bar{x} \pm SD$; * p < 0,01; Student-t-Test zwischen beiden Gruppen.

Chronische Wirkung von Zigarettenrauch

Wenn die Exposition gegenüber Zigarettenrauch in gleicher Intensität wiederholt erfolgt, sind zunehmend bereits die Ausgangswerte für die Aggregabilität der Plättchen pathologisch verändert. Die Beeinflussung durch Passivrauchen ist jedoch im Trend sowohl für die Plättchenfunktion als auch das Prostaglandinsystem eher schwächer ausgeprägt. Auch hier ist der Einfluß auf βTG und PF4 geringer als auf die übrigen Parameter (Tabelle 1). Nach 5 Tagen täglicher Rauchexposition unter den beschriebenen standardisierten Bedingungen nähern sich die basalen Werte für die Plättchensensitivität der Nichtraucher denen der Raucher kontinuierlich an, während sich in der Rauchergruppe selbst keine signifikante Veränderung nachweisen läßt (Tabelle 2).

Diskussion

Nitrosamine sind im Nebenstrom in eindeutig höherer Konzentration als im Hauptstrom enthalten. Aus inhaliertem Zigarettenrauch (sowohl aktiv als auch passiv Rauchende) wird praktisch das gesamte Nikotin über das Alveolarendothel resorbiert und erreicht in erster Linie unmittelbar Herz und Gehirn, wo eine Besetzung von Rezeptoren mit jedem Zug bis zum „steady state“ stattfindet. Da die Halbwertszeit von Nikotin jedoch unter 2 Stunden liegt, sind länger anhaltende Veränderungen, wie z. B. der Thrombozytenfunktion, nicht mehr durch direkten Nikotineinfluß erklärbar [21]. Der um eine Zehnerpotenz niedrigere Benzolgehalt in der Atemluft von Passivrauchern im Vergleich zu Aktivrauchern läßt einen groben Vergleich zwischen aktivem und passivem Rauchen zu. Es scheint, daß Raucher im Sinne einer Toleranzentwicklung gegenüber Nikotin eine permanent pathologisch verminderte Plättchensensitivität gegenüber antiaggregatorisch wirkenden Prostaglandinen aufweisen. Das Thromboembolierisiko entwickelt sich bei Rauchern kontinuierlich und auf lange Sicht. Chronisches Rauchen kann die Plättchen gegenüber PGI₂ desensibilisieren [22, 23], was sich in einer gesteigerten Aggregationsbereitschaft (Thrombusbildung) widerspiegelt. Für passive Raucher (Mitrau-

cher) hingegen besteht diese Gefahr ebenfalls, allerdings wesentlich schneller, hält jedoch nur relativ kurze Zeit an. Obwohl kein direkter Beweis existiert, besteht doch ein potentiell Risiko, besonders in Kombination mit anderen Risikofaktoren, wie z. B. Hypercholesterinämie, „Pille“, Doping sowie bei maximaler anaerober Belastung. Es handelt sich dabei um eine Kette von Zusammenhängen, die sicherlich in Abhängigkeit von Frequenz und Intensität der Exposition eine Schädigung wahrscheinlich macht. Über eine mögliche unterschiedliche Toleranz und Abwehrkapazität der genannten Systeme gegenüber Passivrauchern ist noch nichts bekannt. Aus den genannten Gründen ist ein direkter Nachweis einer auf Passivrauchern zurückzuführenden Schädigung wohl kaum jemals weder naturwissenschaftlich im Einzelfall noch statistisch epidemiologisch zu führen. Die Befunde zeigen, daß durch Passivrauchen der Nichtraucher zum Raucher wird. Das Ausmaß der Veränderungen zeigt eine signifikante Belastung des Hämostasesystems an, aber eine gesicherte Schädigung kann wegen der hohen Reservekapazität des Organismus nicht sicher bewiesen werden.

Ausblick

Obwohl keine definitive Aussage über die Langzeitfolgen von passivem Rauchen auf die genannten Parameter der Plättchenfunktion bzw. das Prostaglandinsystem und damit auf die Entstehung atherosklerotischer Veränderungen möglich ist, sprechen die bisher bekannten Befunde, v. a. die Befunde am Ungeborenen, dafür, daß die passive Konfrontation mit Zigarettenrauch, neben psychosozialen Aspekten, im Einzelfall auch gefäßschädigend und gesundheitsgefährdend sein kann.

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Über die Regression atherosklerotischer Läsionen

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Summary: Regression of atherosclerotic lesions

Summary: The regression of even advanced atherosclerotic vascular lesions is now well-documented in various animal species (dogs, pigs, rabbits, birds and monkeys). In man, well-controlled studies in selected groups of patients have already shown that a reduction of luminal stenosis may take place. After a reliable morphological and morphometric validation has been obtained, non-invasive and easily applicable methods are available which allow reproducible documentation of the reduction in lesions.

Key words: Atherosclerosis, regression.

Zusammenfassung: Die Rückbildung atherosklerotischer Läsionen auch ausgeprägter Natur ist heute bei verschiedenen Spezies (Hund, Schwein, Kaninchen, Vogel und Affen) dokumentiert. Beim Menschen haben kontrollierte Studien in selektierten Gruppen von Patienten gezeigt, daß eine Reduktion einer Stenose erreicht werden kann. Nach guter morphologischer und morphometrischer Validisierung stehen nichtinvasive, leicht reproduzierbare Methoden zur Verfügung, die eine sichere Dokumentation der Reduktion von Läsionen erwarten lassen.

Schlüsselwörter: Atherosklerose, Rückbildung.

Einleitung

Durch gut dokumentierte Untersuchungen [24] auf experimentellem Niveau bei verschiedenen Spezies (Hund [12], Schwein [11], Kaninchen [32, 39], Vogel [9]),

ebenso wie bei Nichtmenschenaffen [4, 18, 19, 27] und einer Reihe von Untersuchungen der Wissler-Gruppe in Chicago nach diätetischen, pharmakologischen und chirurgischen (partieller Ileum-Bypass) Behandlungen [40-43] scheint die Rückbildung parietaler atherosklerotischer Läsionen auch beim Menschen nachweisbar zu sein. Im Rahmen eines Reviews von C.J. Glueck [15] des Lipid Research Clinics Coronary Primary Prevention Trial und der Oslo-Heart-Studie wird berichtet, daß im „Leiden Interventional Trial“ ein Stoppen des Wachstums der koronar-atherosklerotischen Läsionen mit der Rate des Gesamtcholesterins zu HDL-Cholesterin korrelierte.

Zuletzt haben Blankenhorn und Mitarbeiter [6] in einer Monographie Planung, Methode und erste Ergebnisse der Cholesterin-Atherosklerosesenkungsstudie (CLAS) mitgeteilt. In einer Zusammenfassung früherer Arbeiten erinnern sie daran, daß 2 generelle Strategien angewandt wurden, um die Wirksamkeit von Medikamenten oder diätetischen Maßnahmen zu prüfen, die ein Fortschreiten atherosklerotischer Läsionen beim Menschen verlangsamen oder eine Rückbildung erreichen sollen. Die erste Strategie ist es, Effekte von Atherosklerose-bezogener Morbidität und Mortalität nachzuweisen. Diese Strategie nimmt an, daß die Effekte der Therapie ausgeprägt genug sind, um trotz der Anwesenheit ausgeprägter Läsionen das bekannte

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Davis, J.W., Shelton, L., Watanabe, I.S. and Arnold, J., "Passive Smoking Affects Endothelium and Platelets," Arch. Intern. Med. 149: 386-389, 1989.

Ten healthy nonsmokers (medical students and physicians) sat for 20 minutes in a hospital corridor where patients typically went to smoke cigarettes. This constituted "passive smoking" or ETS exposure. Blood values before and after these 20 minute periods were compared to those obtained during a control period, when the subjects simply sat for 20 minutes in a laboratory room where smoking was prohibited.

The authors reported that ETS exposure was associated with increased platelet aggregation, as well as with an increase in the number of anuclear endothelial cell carcasses in the blood. Both of these effects were considered to be important mechanisms involved in atherosclerosis and arterial thrombosis. These effects on platelets and endothelial cells were described as being similar to those observed with "active" smoking.

Comment

This report suffers from a variety of important flaws. It involves a very small number of subjects (only 10) and no females. Furthermore, there was no true control condition in this study, which raises the possibility that a variety of potential confounding factors may have influenced the results. That is, ETS exposure was in a hospital corridor, whereas the nonexposure

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condition was in a laboratory. These are entirely different environments, involving social factors, noise factors, ventilation factors, and a variety of other differences.

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Passive Smoking Affects Endothelium and Platelets

James W. Davis, MD; Loretta Shelton;
Itaru S. Watanabe, MD; Joyce Arnold

Blood was obtained before and after ten healthy male nonsmokers sat for 20 minutes in open hospital corridors beside men who were already there smoking by their own initiative. Mean values before and after passive smoking were 0.87 and 0.78 for the platelet aggregate ratio, 2.8 and 3.7 per cent for the endothelial cell count, 0 and 2.8 ng/mL for the plasma nicotine concentration, and 0.9% and 1.3% for the carboxyhemoglobin level. No variable changed significantly during control periods in which the subjects sat in a room where smoking was prohibited. Passive exposure to tobacco smoke affected the endothelial cell count and platelet aggregate ratio in a manner similar to that previously observed with active smoking.

(Arch Intern Med 1989;149:396-399)

Cigarette smoking has a strong epidemiologic association with atherosclerosis, myocardial infarction, occlusive peripheral vascular disease, and stroke.¹⁻⁴ Both endothelial damage and platelet activation are thought to be important in the pathogenesis of atherosclerosis and arterial thrombosis,^{5,6} and to occur as a response to cigarette smoking.⁷ Pterovský and Hladovec⁷ reported that the concentration of anuclear carcasses of endothelial cells in venous blood increased after cigarette smoking. Their observations have been confirmed in our laboratory, where the mean endothelial cell counts of healthy male and female naive smokers approximately doubled after smoking two tobacco cigarettes and did not change significantly after sham smoking.⁸ We observed similar effects when male habitual smokers with⁹ and without¹⁰ coronary artery disease smoked. Enhanced platelet aggregate formation after active smoking has been observed in several studies.¹¹⁻¹³

Passive smoking involves breathing both sidestream smoke that goes directly into the air from the burning end of tobacco products and mainstream smoke after it has been exhaled by smokers. Sidestream smoke has higher concentrations of several potentially noxious compounds

than mainstream smoke, with the ratio of sidestream to mainstream carbon monoxide reported to be 4.7.¹⁴ The present study was done to determine whether passive smoking in a naturally occurring environment has acute effects on the endothelium and platelets similar to those of active smoking.

METHODS

Subjects and Experimental Design

After an overnight fast, ten healthy male medical students and physicians, who were nonsmokers and had a mean age of 28 years (age range, 23 to 49 years), participated in two 20-minute experimental periods. The experiments took place in the morning before work to avoid exposure to environmental smoke before the experimental periods began. The periods were separated by one week, with five men having a control period first and five men having a passive smoking period first. The men did not take medicines on a regular basis and were prohibited from taking aspirin or other nonsteroidal anti-inflammatory agents from ten days before the first experimental period until completion of the second period. Control periods consisted of sitting in the laboratory where smoking was prohibited, and passive smoking periods consisted of sitting where several patients had come to smoke of their own accord in chairs placed against the length of one wall opposite elevators where a 1110 × 480-cm atrium with a 240-cm ceiling connected with corridors at each end by a 225-cm opening. When there was an unoccupied seat between two men who were smoking, the experimental subject sat there. Sometimes, the subject sat beside only one man who was smoking, because there was no unoccupied seat between two smokers. Antecubital venipunctures were done in the laboratory before and after each experimental period to obtain blood for determination of the platelet aggregate ratio, the endothelial cell count, the plasma nicotine concentration, and the carboxyhemoglobin level.

Platelet Aggregate Ratio

Our modification¹⁵ of the method of Wu and Hoak¹⁶ was used. The method is based on the ratio of the platelet count of platelet-rich plasma, prepared from blood that had been mixed immediately after venipuncture with a solution containing edetic acid (EDTA) and formaldehyde, to that of platelet-rich plasma prepared in the same manner, except for the absence of formaldehyde. Wu and Hoak¹⁶ theorized that platelet aggregates circulating in blood are fixed when drawn into a solution that contains formaldehyde and edetic acid and break apart when drawn into a solution that contains edetic acid without formaldehyde. The data of others¹⁷⁻¹⁹ suggest that the platelet aggregate ratio is also influenced by aggregates formed during the withdrawal of blood through a needle and tubing. In any case, a decrease in the platelet aggregate ratio reflects an increased formation of platelet aggregates. In the present study, the length of the plastic tubing through which blood

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was withdrawn was 8.9 cm rather than the 30-cm length used in our previous studies.¹⁴

Endothelial Cell Counts (Counts of Anuclear Endothelial Cell Carcasses)

The method of Hladovec and Rossmann¹⁵ was used. Nine milliliters of venous blood was collected in a siliconized centrifuge tube that contained 1 mL of 3.8% trisodium citrate and mixed. Centrifugation at 4°C and 396 g (middle of the tube) for 20 minutes removed the erythrocytes and leukocytes. One milliliter of the supernatant was mixed with 0.2 mL of adenosine 5'-diphosphate, disodium salt (1 mg/mL) and mechanically shaken for ten minutes. Another centrifugation at 396 g for 20 minutes removed the platelet aggregates. The supernatant was then centrifuged at 2100 g for 20 minutes. After suspension of the sediment in 0.1 mL of physiologic saline by stirring with a siliconized glass rod, four Neubauer chambers were filled with the suspension, and the endothelial cells were counted using phase-contrast microscopy. Results were expressed as the mean cell count of the four 0.9- μ L chambers.

On two occasions, we evaluated the possibility that the cells counted as endothelial cells might instead be megakaryocyte fragments. The cells were transferred from the saline suspensions to glass slides by centrifugation (Cytospin, Shandon Southern Instruments, Inc, Birmingham, Ala). The slides were incubated for 45 minutes with mouse monoclonal anti-human platelet glycoprotein Ib antibody (Dako Corp, Santa Barbara, Calif) that was diluted in phosphate-buffered saline to a concentration of 16.5 μ g of antibody protein per milliliter, washed with phosphate-buffered saline, incubated for 45 minutes with goat anti-mouse IgG fluorescein conjugate (Boehringer Mannheim, Indianapolis) that was diluted to a concentration of 94 μ g of antibody protein per milliliter, and washed again. Fluorescence microscopy revealed no fluorescence of the endothelial cell preparations, while simultaneously processed slides on which human bone marrow aspirates had been smeared showed strong fluorescence of large cells that were presumed to be megakaryocytes.

Plasma Nicotine

A portion of the platelet-rich plasma, prepared in the first centrifugation in the procedure for endothelial cell counting, was kept frozen at -80°C until it was thawed for extraction and preparation for gas chromatography by the method of Feyerabend and Russell,¹⁶ using an instrument that was equipped with a nitrogen-phosphorus detector (Aerograph 1400, Varian Instruments Division, Walnut Creek, Calif). The length of the column was 90 cm. Column temperature was 150°C. The method was not otherwise modified from the original.¹⁶ The means of duplicate assays of each sample of plasma were used for statistical analysis.

Carboxyhemoglobin

Blood was taken into a heparinized syringe for determination of the carboxyhemoglobin level by spectrophotometry (11-222 CO-oximeter, Instrumentation Laboratories, Lexington, Mass).

Statistical Analysis

Two-tailed Wilcoxon signed-rank tests were used to determine the significance of the differences between the means of the paired variables shown in the Table and in Figs 1 through 4. Confidence intervals of the differences were calculated according to Gardner and Altman.¹⁷ The Spearman rank correlation coefficient was used as a measure of the association between variables.

RESULTS

The Table shows the mean values of each variable before and after the control period. No significant differences occurred ($P > .2$ for each comparison).

Figure 1 shows that the platelet aggregate ratio of each of the ten subjects was lower after than before passive smoking. The mean values (± 1 SD) were 0.87 ± 0.06 before and 0.78 ± 0.07 after passive smoking, with a mean difference of 0.09 and a 95% confidence interval of 0.03 to 0.15.

Figure 2 shows that the endothelial cell count was always

Mean Values (± 1 SD) of Variables Before and After Control Period		
Variable	Mean (± 1 SD)	
	Before	After
Platelet aggregate ratio	0.88 (± 0.06)	0.88 (± 0.04)
Endothelial cell count	2.2 (± 0.8)	2.3 (± 1.0)
Plasma nicotine concentration, ng/mL	0	0
Blood carboxyhemoglobin level, %	1.1 (± 0.8)	1.2 (± 0.7)

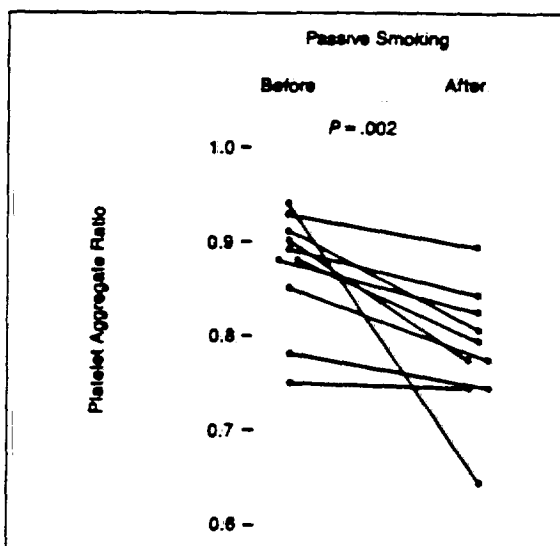


Fig 1.—Platelet aggregate ratios before and after passive smoking.

higher after than before passive smoking. Mean values (± 1 SD) before and after were 2.8 ± 0.9 and 3.7 ± 1.1 per counting chamber, respectively, with a mean difference of 0.9 per chamber and a 95% confidence interval of 0 to 1.8 per chamber.

Figure 3 shows that nicotine was not detectable in the plasma of any subject before passive smoking and was present in the plasma of all but one subject after completion of the 20-minute period of passive smoking. The mean concentration (± 1 SD) after passive smoking was 2.8 ± 1.2 ng/mL.

Figure 4 shows that the carboxyhemoglobin level was higher after passive smoking in all but one subject, whose value was unchanged. Mean values (± 1 SD) were $0.9\% \pm 0.3\%$ before and $1.3\% \pm 0.6\%$ after passive smoking, with a mean difference of 0.4% and a 95% confidence interval of 0% to 0.8%.

After passive smoking, the percent carboxyhemoglobin level did not correlate significantly ($P > .60$) with the platelet aggregate ratio or the endothelial cell count. The correlation coefficient between the change in the carboxyhemoglobin level from before to after passive smoking and the corresponding change in the endothelial cell count was .78 ($P < .01$), while the change in the carboxyhemoglobin level was not significantly ($P > .30$) correlated with that of the platelet aggregate ratio. Neither the plasma nicotine concentration after passive smoking nor its change from

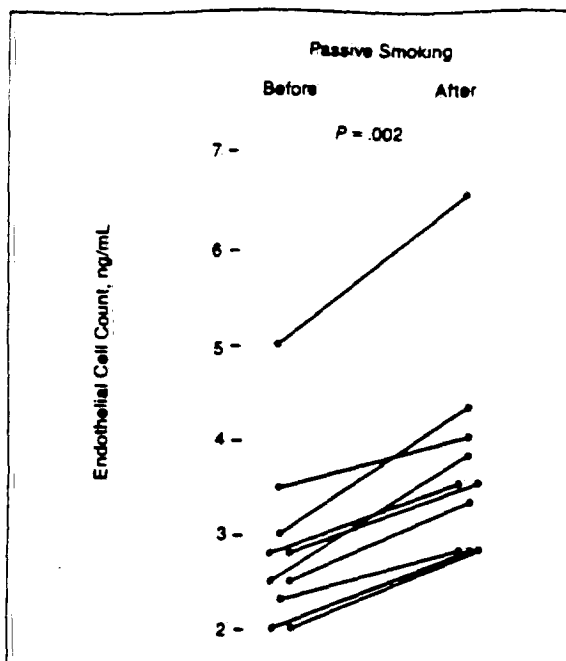


Fig 2.—Endothelial cell counts before and after passive smoking.

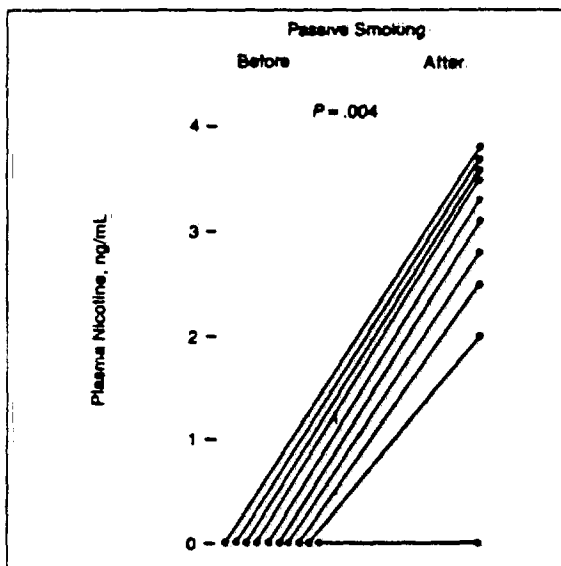


Fig 3.—Plasma nicotine concentrations before and after passive smoking.

before to after passive smoking was significantly ($P > .20$) correlated with the corresponding values of the platelet aggregate ratio or the endothelial cell count.

COMMENT

Hladovec and Rossmann¹⁷ described a simple method for the quantitation of anuclear carcasses of endothelial cells in blood. The identity of endothelial cells was based on

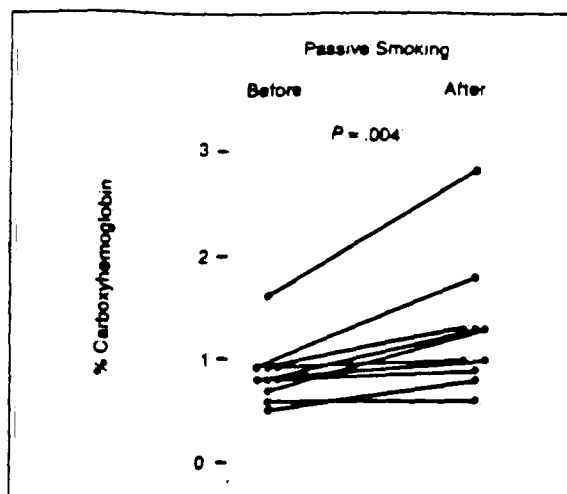


Fig 4.—Carboxyhemoglobin levels before and after passive smoking.

their morphologic similarity to cells that were scraped from the endothelium, with the exception that the cells isolated from blood had no nuclei. Takahashi and Harker¹⁸ added cultured human endothelial cells to blood and recovered them from mononuclear cell fractions in which they were identified by the presence of factor VIII-related antigen as a cell marker. They detected no endothelial cells in mononuclear cell fractions of venous blood from ten normal subjects. Using the method of Hladovec and Rossmann,¹⁷ we^{1,2} found endothelial cells in the venous blood of normal men and women and men with coronary artery disease. Since, like Hladovec and Rossmann,¹⁷ we saw no nuclei in these cells, there is no conflict with the report of Takahashi and Harker¹⁸ of the absence of endothelial cells from mononuclear cell fractions. In a previous study,¹ we identified the anuclear cells as endothelial by their fluorescence after incubation with fluorescein-labeled anti-human factor VIII-related antigen antibody and by the lack of fluorescence of the epithelium in simultaneously incubated sections of human skin.

The present study, showing that brief passive exposure to tobacco smoke under naturally occurring environmental conditions has consistent acute effects on the endothelium and platelets, was limited to a group of ten healthy male nonsmokers. It seems likely that this small group may be representative of the general population since we observed similar effects of active smoking on healthy male and female naive smokers,¹ healthy male² and female (J.W.D. and L.S., unpublished data, 1982) habitual smokers, and male habitual smokers with coronary artery disease.^{1,2} Other workers have shown that passive smoking by non-smokers lowers platelet sensitivity to the antiaggregatory effect of prostacyclin.¹⁹

Although a statistically significant correlation between the change in the endothelial cell count and the change in the carboxyhemoglobin level from before to after passive smoking was found, there was not a significant correlation between these variables after passive smoking. We previously found that smoking tobacco cigarettes had a much greater effect on both platelets and the endothelium than did smoking cigarettes that contained no nicotine.¹ The relative importance of carbon monoxide, nicotine, and the many other components of tobacco smoke as causes of the

observed effects on platelets and the endothelium remains unclear.

The significance of enhanced platelet aggregate formation and an increased concentration of anuclear carcasses of endothelial cells in blood after passive smoking is not known. However, both platelet activation⁴ and endothelial damage⁵ are prominent among the mechanisms thought to be involved in atherosclerosis and arterial thrombosis. Epidemiologic studies are needed to determine whether repeated episodes of passive exposure to tobacco smoke during a period of years enhance the development of atherosclerosis and its complications in nonsmokers. A large Japanese study²² indicated that nonsmoking wives of

heavy smokers had a higher risk of developing lung cancer, while the husbands' smoking habit did not affect their wives' risk of dying of ischemic heart disease. Stock²³ suggested that Japanese people may be protected from fatal coronary heart disease by a high dietary intake of eicosapentaenoic acid. We hope that our work will be an impetus to the development of epidemiologic investigations of a possible relationship between passive smoking and vascular diseases in Western countries.

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Moskowitz, W.B., Mosteller, M., Schieken, R.M., Bossano, R., Hewitt, J.K., Bodurtha, J.N. and Segrest, J.P., "Lipoprotein and Oxygen Transport Alterations in Passive Smoking Preadolescent Children: The MCV Twin Study," Circulation 81(2): 586-592, 1990.

This is a statistical study attempting to determine potential relationships between several blood chemistry values of preadolescent children in relation to parental smoking habits. The authors reported that ETS exposure from the parents was associated with elevations in 2,3-diphosphoglycerate (2,3-DPG). ETS exposure was also reported to be associated with decreases in certain HDL subfractions. The data regarding 2,3-DPG were characterized as indicating that ETS exposure induces a hypoxic state. Elevations in 2,3-DPG thus reflect an attempt by the body to compensate for this hypoxia. The significance of the changes in HDL levels stems from reports that the incidence of atherosclerotic heart disease is associated with decreased levels of HDL.

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Lipoprotein and Oxygen Transport Alterations in Passive Smoking Preadolescent Children

The MCV Twin Study

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We investigated the cardiovascular effects of lifelong passive cigarette smoke exposure in preadolescent children and examined the following questions: 1) Is systemic oxygen transport altered? 2) Are coronary heart disease risk factors adversely affected? We recruited 216 families from the MCV Twin Study; 105 had at least one smoking parent. Serum thiocyanate and cotinine levels were used as measures of smoke exposure in the children and thiocyanate was proportional to the number of parental cigarettes smoked each day ($p=0.0001$). Paternal smoking had no effect on these measures. Whole blood 2,3-diphosphoglycerate was higher in smoke-exposed than unexposed children ($p<0.01$) and was related to the thiocyanate level ($p<0.02$). High density lipoprotein (HDL) cholesterol was lower in passive smoking children ($p<0.05$); the HDL₂ subfraction was reduced in passive smoking boys, while the HDL₂ subfraction was reduced in passive smoking girls. Significant adverse alterations in systemic oxygen transport and lipoprotein profiles are already present in preadolescent children exposed to long-term passive cigarette smoke, primarily from maternal smoke. Children with long-term exposure to passive smoke may be at elevated risk for the development of premature coronary heart disease. (*Circulation* 1990;81:586-592)

The adverse health effects of actively inhaled cigarette smoke include impaired pulmonary function, increased coronary and cerebrovascular disease, chronic pulmonary disease, and cancer.¹⁻³ Cigarette smoking is a powerful independent risk factor for myocardial infarction, sudden death, peripheral vascular disease, and stroke and is the most important of the modifiable risk factors for coronary heart disease.⁴ The greatest relative risk related to smoking occurs in younger age groups,⁵ and an unusually high proportion of individuals with premature coronary heart disease are smokers.⁶ Therefore, smoking is an important risk factor associated with premature coronary heart disease.

Infants and young children of smoking parents who are passively exposed to cigarette smoke are more at risk for lower respiratory tract infections and small airway disease than are children of nonsmoking parents.^{7,8} What is less clear is whether the cardiovascular and oxygen transport systems of the growing child are adversely affected by long-term exposure to passive inhalation of cigarette smoke. Atherosclerotic changes found in middle-aged men may begin in childhood where certain risk factors are thought to be related to the earliest stages of atherosclerotic disease.^{9,10} Therefore, we asked the following questions: 1) Is systemic oxygen transport altered in chronically exposed passive smoking children of active smoking parents? 2) If abnormalities exist, are they related to the amount of cigarette smoke exposure? 3) Does passive cigarette smoking in preadolescent children detrimentally alter their coronary heart disease risk factors? To answer these questions, we evaluated the systemic oxygen transport variables, coronary risk factors, and echocardiographic cardiovascular measurements of 216 pairs of preadolescent twins from smoking versus nonsmoking families.

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Methods

Population

As part of an ongoing genetic longitudinal study of developmental changes in cardiovascular risk factors during adolescence, we recruited families with twins from nearby school systems. Eleven-year-old twins were ascertained from more than 75 middle schools of central Virginia within a 150-mile radius with use of a computerized population-based registry. Information packets were mailed to the schools for distribution to parents of twins to maintain confidentiality from the investigators. The parents who replied by mail (50%) were invited to participate.

The families participated in a protocol that included the collection of data on family health histories, smoking history (historical data provided by parents), blood pressure, electrocardiographic measurements, echocardiographic measurements, and the collection of blood samples for biochemical assays. The number of cigarettes smoked each day by the parents was recorded. No attempt was made to prescreen enrollees for the presence or absence of cardiovascular risk factors. Informed written consent, which had been approved by the Committee on the Conduct of Human Research of the Virginia Commonwealth University, was obtained from each family before it entered the study.

Procedures

Anthropometrics and blood pressure. Height and weight of each subject in stocking feet were measured with a stadiometer and digital scale, respectively. Sexual maturation was self-assessed by asking each subject to select a drawing of the Tanner stage of pubic hair development that most closely corresponded to his or her own level of sexual development.¹¹ Two resting blood pressure measurements were obtained with the subject in a sitting position using a mercury sphygmomanometer and the appropriately sized compression cuff. The fourth Korotkoff phase was recorded as the diastolic blood pressure.

Echocardiography. Echocardiographic left ventricular wall thicknesses and chamber dimensions were measured according to standardized measurement criteria.¹² Echocardiograms were obtained with the subject in the recumbent position using an SKI ultrasonoscope 20'A with a 3.5 MHz probe and Honeywell 1856 strip-chart recorder. Echocardiograms were obtained and read in a blinded fashion; the individuals performing and reading the echocardiograms were not aware of the passive smoking status of the children. The echocardiographic tracings were placed over a bit pad and using a microcomputer, digitized echocardiographic dimensions, wall thicknesses, and heart rate were measured and stored on diskette. The measurements were not adjusted for heart rate. The data from the diskette were transferred to a computer where the echocardiographic-derived variables were calculated.¹³

Blood samples. A sample of whole blood was obtained, stored on ice, and processed within 1 hour for quantitative lipoprotein cholesterol measurements using the vertical spin ultracentrifugation technique.¹⁴ Quantitative lipoprotein cholesterol levels were obtained on all but five nonsmoking and three passive smoking twin pairs. Hematocrit was determined in duplicate by capillary tube centrifugation. Early in the study, we obtained the techniques to measure whole blood thiocyanate level ($n=108$ twin pairs) and red blood cell 2,3-diphosphoglycerate level (2,3-DPG) ($n=163$ twin pairs). Blood thiocyanate concentration was determined by a quantitative colorimetric method at 450 nm^{15,16} and red cell 2,3-DPG level was determined by the method of Fiske and SubbaRow.¹⁷ Serum cotinine concentration was quantitated by radioimmunoassay methods.^{18,19}

Data Analysis

Data are presented as mean \pm SD. Statistical differences between group means were assessed by two-sided t tests, taking into account whether group variances were equal. Because twins share genes and environments and represent nonindependent observations, data from only a single twin randomly ascertained from each family was used to determine group means for statistical testing. Nonparametric correlation coefficients using the Kendall Tau B statistic were used when it was apparent that a given variable was not normally distributed, such as cigarettes smoked each day, serum thiocyanate, and high density lipoprotein (HDL) cholesterol. Regression analysis was used to remove the effects of confounding variables.

Group means for passive smoking and nonsmoking subjects were adjusted to correct for differences in age, height, weight, and, when the groups included both males and females, sex. A multiple linear regression analysis was conducted in which the response variable was modelled as a linear function of the above covariates. Regression coefficients were obtained and the expected value of the response variable was calculated with the covariates fixed to their mean values. These adjustment computations were carried out using the LSMEANS option of the General Linear Models procedure of the SAS statistical package. The heritability of specific variables was estimated as two times the difference of the twin correlations in monozygotic and dizygotic pairs.²⁰ All results were considered statistically significant at $p < 0.05$.

Results

Smoking data were available on 216 families enrolled in the MCV Twin Study. One hundred eleven of these families had nonsmoking parents. Of these nonsmoking families, both parents were never smokers in 50, the father smoked in the past in 25, the mother smoked in the past in nine, and in 27 both parents smoked in the past. Of the mothers who smoked in the past, 21 smoked during the pregnancy of the twins. Fathers who smoked in the past stopped

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smoking 10.0 ± 6.7 years before evaluation, though five stopped smoking within 1 year of the study. Mothers who smoked in the past stopped smoking 8.6 ± 7.3 years before evaluation with seven stopping within 1 year of the study.

In 105 families, either or both parents were cigarette smokers at the time of evaluation, and maternal smoking during pregnancy occurred in 69 of these. In the 105 smoking families, the father was the only smoker in 44%, the mother in 32%, and both parents were smokers in 24%. The fathers began smoking at 18.2 ± 6.2 years of age and presently smoke 24.5 ± 12.6 cigarettes/day. The mothers began smoking at 18.4 ± 4.3 years of age and presently smoke 18.5 ± 9.7 cigarettes/day. The total daily number of cigarettes smoked by the parents ranged from 1 to 10 in 17%, 11 to 20 in 32%, and was greater than 20 in 51%.

Data were obtained and analyzed on 105 passive smoking twin pairs and 111 non-passive smoking twin pairs. Of the non-passive smoking twin pairs, 61 were monozygotic and 50 were dizygotic, while of the passive smoking twin pairs, 55 were monozygotic and 50 were dizygotic. None of the twins had ever smoked cigarettes.

Indexes of passive cigarette smoke exposure were obtained by measuring serum levels of cotinine and thiocyanate. The passive smoking twins ($n=35$) demonstrated higher levels of thiocyanate than the non-passive smoking twins ($n=89$) (7.1 ± 4.3 vs. 3.1 ± 3.0 mg/L, $p < 0.0001$). Passive smoking boys and girls had similar elevations of thiocyanate (7.0 ± 4.1 and 7.3 ± 4.5 mg/L, respectively). Cotinine was not detected in non-passive smoking twins but was present in passive smoking twins (1.5 ± 3.1 ng/ml), and serum thiocyanate level correlated with the cotinine level ($r=0.44$, $p < 0.005$). The level of thiocyanate in non-passive smoking twins is best explained by non-tobacco dietary sources of thiocyanate as we can exclude the possibility of significant smoke exposure outside their homes due to the absence of cotinine in their blood. The intrawin pair correlation for thiocyanate was high ($r=0.94$, $p < 0.0001$), demonstrating that twins within a smoking family generally have similar exposure to home environmental cigarette smoke.

Within all smoking families, thiocyanate level correlated with the total number of cigarettes smoked each day ($r=0.35$, $p < 0.0001$). In a subgroup of smoking families in which the mother but not the father smoked ($n=14$), there was good correlation between thiocyanate level in the twins and the number of cigarettes smoked each day by the mother ($r=0.57$, $p < 0.01$) (Figure 1), whereas in families in which the father was the only smoker ($n=38$), no correlation was found. This suggests that paternal cigarette smoking provides little or no contribution to the home passive smoking environment and that maternal cigarette smoking is the major source of child-home passive smoke exposure.

The unadjusted data on passive smoking and non-passive smoking groups as a whole and separated by

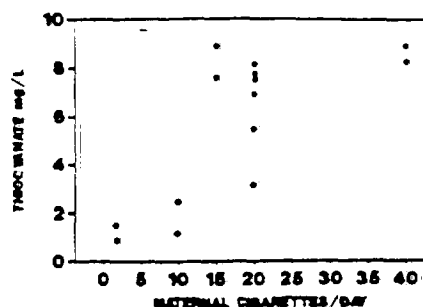


FIGURE 1. Plot of the relation of child serum thiocyanate level to number of cigarettes smoked each day by the mother. Plotted points represent data from 14 passive smoking children. Kendall Tau B correlation coefficient = 0.57, $p < 0.01$.

sex are presented in Table 1, while variables of interest after adjustment for age, height, weight, and sex are presented in Table 2. Passive smoking and nonsmoking groups were similar for age, Tanner stage, height, systolic blood pressure, and diastolic blood pressure. Girls were more advanced in sexual development by Tanner stage than boys in both non-passive smoking and passive smoking groups ($p < 0.01$). Passive smoking children weighed slightly more than non-passive smoking children.

The hematologic data on passive smoking and non-passive smoking groups are shown in Tables 1 and 2. The mean hematocrit value was similar for the two groups. Passive smoking children had higher whole blood levels of 2,3-DPG. While this difference was significant in the boys, a similar trend was present in the girls. In smoking families, the 2,3-DPG level correlated directly with the serum thiocyanate level and the total number of cigarettes smoked by the parents (both, $p < 0.05$). The relation between the 2,3-DPG level and the serum thiocyanate level in passive smoking children ($r=0.29$, $p < 0.02$) is shown in Figure 2.

Quantitative lipoprotein cholesterol levels are presented in Tables 1 and 2. The mean time elapsed from the last meal to the time of blood drawing was 6.3 hours and was similar for passive smoking and non-passive smoking groups. In our population, the duration of fasting did not contribute to the variance of either total cholesterol or lipoprotein levels.²¹ The passive smoking group had significantly lower total cholesterol than the non-passive smoking group. Passive smoking boys had slightly higher total cholesterol and low density lipoprotein (LDL) cholesterol levels than non-passive smoking boys, though these differences were not statistically significant. However, passive smoking girls had significantly lower levels of total cholesterol and LDL cholesterol when compared with non-passive smoking girls.

Significant intergroup differences were seen in the HDL cholesterol subfractions. Total HDL cholesterol was lower in the passive smoking group when compared with the non-passive smoking group, even after adjusting for age, weight, height, and sex. This

TABLE 1. Unadjusted Mean \pm SD for Passive Smoking and Nonsmoking Twin Groups

	All twins		Boys		Girls	
	Nonsmoking (n=111)	Passive smoking (n=105)	Nonsmoking (n=56)	Passive smoking (n=50)	Nonsmoking (n=55)	Passive smoking (n=55)
Age	11.8 \pm 1.2	11.9 \pm 1.2	12.0 \pm 1.4	11.8 \pm 1.1	11.6 \pm 1.0	11.9 \pm 1.3
Tanner	2.6 \pm 1.2	2.7 \pm 1.3	2.5 \pm 1.2	2.4 \pm 1.2	2.8 \pm 1.3	3.0 \pm 1.3
Height (cm)	149.1 \pm 9.9	150.5 \pm 9.1	150.0 \pm 11.4	149.8 \pm 9.1	148.2 \pm 8.2	151.1 \pm 9.1
Weight (kg)	39.8 \pm 8.9	43.1 \pm 11.3*	40.1 \pm 9.1	43.2 \pm 11.8	39.6 \pm 8.8	43.0 \pm 10.9
Heart rate (beats/min)	72.9 \pm 12.5	72.6 \pm 12.4	67.7 \pm 9.2	69.1 \pm 10.5	77.7 \pm 13.3	76.2 \pm 13.3
SBP (mm Hg)	106.9 \pm 9.9	109.1 \pm 9.6	106.3 \pm 10.5	110.1 \pm 10.6	107.5 \pm 9.2	108.2 \pm 8.6
DBP (mm Hg)	59.5 \pm 11.5	61.5 \pm 10.8	57.8 \pm 11.4	61.0 \pm 13.0	61.2 \pm 11.4	62.0 \pm 8.6
Hematocrit (%)	39.8 \pm 1.9	39.5 \pm 2.2	40.0 \pm 1.9	40.0 \pm 2.5	39.6 \pm 1.8	39.1 \pm 1.8
DPG (μ m/ml)	1.98 \pm 0.28	2.08 \pm 0.23*	1.89 \pm 0.26	2.08 \pm 0.23*	2.05 \pm 0.27	2.08 \pm 0.24
Cholesterol (mg/dl)	172.8 \pm 24.8	164.3 \pm 29.5*	168.2 \pm 22.0	170.1 \pm 31.2	177.4 \pm 26.8	158.6 \pm 26.8
LDL (mg/dl)	86.5 \pm 19.5	81.7 \pm 21.8	81.6 \pm 17.8	85.0 \pm 23.2	91.4 \pm 20.1	78.5 \pm 20.0
HDL (mg/dl)	49.5 \pm 9.3	45.7 \pm 10.4†	49.3 \pm 8.8	45.2 \pm 9.6*	49.7 \pm 9.7	46.1 \pm 11.2
HDL ₂ (mg/dl)	13.9 \pm 7.4	12.1 \pm 7.1	13.6 \pm 7.2	10.8 \pm 6.3*	14.2 \pm 7.6	13.2 \pm 7.7
HDL ₃ (mg/dl)	35.7 \pm 6.5	33.6 \pm 5.8*	35.8 \pm 5.4	34.4 \pm 5.8	35.5 \pm 7.6	32.8 \pm 5.8*
L/H	1.80 \pm 0.52	1.88 \pm 0.67	1.70 \pm 0.47	1.95 \pm 0.64*	1.90 \pm 0.55	1.81 \pm 0.69
LVM (g)	90.8 \pm 18.5	99.1 \pm 21.5*	96.8 \pm 19.1	104.7 \pm 20.7	85.4 \pm 16.4	93.9 \pm 21.4

DBP, diastolic blood pressure; DPG, 2,3-diphosphoglycerate; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; L/H, LDL/HDL ratio; LVM, left ventricular mass; SBP, systolic blood pressure.

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

comparison is shown in Figure 3. The LDL/HDL ratio was significantly elevated in the passive smoking boys, though the difference lost significance ($p = 0.06$) after the data were adjusted. The HDL₂ cholesterol subfraction level was consistently lower in all the passive smoking groups but this difference reached significance only for the unadjusted levels in the boys. An inverse trend was found between the total number of cigarettes smoked daily by the mothers and the serum HDL cholesterol level in the children. The lowest HDL₂ cholesterol levels were found in boys exposed to the highest number of cigarettes smoked daily by their mothers. These differences however did not meet statistical significance. The HDL₃ subfraction was significantly lower in the passive smoking group than the non-passive smoking group, with greater differences seen in the girls.

Because of the observed influence of maternal but not paternal cigarette smoking on oxygen transport and lipoprotein profiles, we investigated the possibility that maternal smoking may have affected children during gestation. We therefore compared the data adjusted for age, height, weight, and sex obtained on one twin per family who never had exposure to cigarette smoke ($n = 33$) to that of twins exposed only during gestation by maternal smoking ($n = 8$). An effect of fetal exposure on the HDL cholesterol level was found with lower HDL cholesterol levels in those children exposed in utero (44.6 ± 2.2 vs. 50.2 ± 1.1 mg/dl, $p < 0.05$), though the sample size was quite small. No other significant differences were found between these groups.

Echocardiograms suitable for measurement were obtained on 74 non-passive smoking and 66 passive smoking twin pairs. Left ventricular internal dimen-

TABLE 2. Mean \pm SD in Passive Smoking and Nonsmoking Twin Groups After Adjustment for Age, Weight, Height, and Sex

	All twins		Boys		Girls	
	Nonsmoking (n=111)	Passive smoking (n=105)	Nonsmoking (n=56)	Passive smoking (n=50)	Nonsmoking (n=55)	Passive smoking (n=55)
DPG (μ m/ml)	1.97 \pm 0.03	2.09 \pm 0.03‡	1.90 \pm 0.04	2.08 \pm 0.04‡	2.03 \pm 0.04	2.10 \pm 0.04
Cholesterol (mg/dl)	172.2 \pm 2.7	164.1 \pm 2.7*	168.9 \pm 3.7	169.8 \pm 3.7	176.6 \pm 3.7	157.6 \pm 3.7‡
LDL (mg/dl)	86.1 \pm 2.0	81.3 \pm 2.0	81.8 \pm 2.8	84.7 \pm 2.9	91.0 \pm 2.7	77.5 \pm 2.7‡
HDL (mg/dl)	49.1 \pm 0.9	46.0 \pm 0.9*	49.1 \pm 1.3	45.5 \pm 1.3	49.2 \pm 1.4	46.4 \pm 1.4
HDL ₂ (mg/dl)	13.5 \pm 0.7	12.5 \pm 0.7	13.2 \pm 0.9	11.3 \pm 0.9	13.9 \pm 1.0	13.5 \pm 1.0
HDL ₃ (mg/dl)	35.6 \pm 0.6	33.5 \pm 0.6*	35.9 \pm 0.8	34.1 \pm 0.8	35.3 \pm 0.9	32.8 \pm 0.9
L/H	1.81 \pm 0.05	1.86 \pm 0.06	1.72 \pm 0.08	1.94 \pm 0.08	1.90 \pm 0.55	1.81 \pm 0.69
LVM (g)	93.6 \pm 1.7	95.9 \pm 1.8	100.9 \pm 2.6	100.2 \pm 2.8	87.3 \pm 2.4	91.4 \pm 2.5

DPG, 2,3-diphosphoglycerate; LDL, low density lipoprotein; HDL, high density lipoprotein; L/H, LDL/HDL ratio; LVM, left ventricular mass. * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

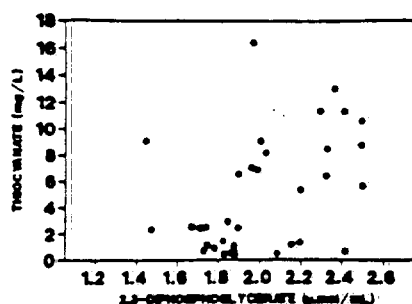


FIGURE 2. Plot of the relation between whole blood 2,3-diphosphoglycerate level and the serum thiocyanate level in passive smoking children ($n=35$): Kendall Tau B correlation coefficient = 0.29, $p < 0.02$.

sions in systole and diastole were the same for the two groups. The passive smoking group was found to have a higher left ventricular mass than the nonsmoking group, though the difference was lost after the data were adjusted for body size (Tables 1 and 2).

Covariates of smoking behavior and other confounding variables were considered, which could have affected the results. When parental income, education level, years of education, and beer and liquor consumption were compared between parents in smoking and nonsmoking families, no differences were found.

When we compared the exercise level (the number of times each week vigorous exercise was performed) in the twins themselves, the number of exercise episodes each week were similar for passive smoking and non-passive smoking boys (4.7 ± 2.0 vs. 4.2 ± 2.3 times/wk) and for passive smoking and non-passive smoking girls (4.3 ± 2.3 vs. 4.7 ± 2.1 times/wk). χ^2 tests showed no association between smoking status and exercise in either the boys ($\chi^2 = 1.7$, $p < 0.2$) or the girls ($\chi^2 = 0.5$, $p < 0.5$).

A preliminary estimate of the heritability of specific variables was obtained using the study's twin

TABLE 3. Intrapair Twin Correlations and Heritability

	Monozygotic ($n=116$)	Dizygotic ($n=100$)	Heritability
WT	0.91	0.57	68%
SBP	0.66	0.33	66%
SCN	0.94	0.91	6%
DPG	0.65	0.41	48%
LDL	0.81	0.35	92%
HDL	0.81	0.42	78%
HDL ₂	0.81	0.36	88%
HDL ₃	0.53	0.50	6%

All monozygotic twin correlations are significant at $p < 0.0001$. All dizygotic twin correlations are significant at $p < 0.005$.

WT, weight; SBP, systolic blood pressure; SCN, thiocyanate; DPG, 2,3-diphosphoglycerate; LDL, low density lipoprotein; HDL, high density lipoprotein.

design. Intrapair twin correlations for identical and nonidentical twins are shown in Table 3. The heritability is indicative of the variation attributable to genetic effects. The correlation for identical twins is significantly higher than for nonidentical twins for all variables except serum thiocyanate and HDL₃ cholesterol levels.

Within sampling error, the monozygotic correlation is twice the dizygotic correlation for systolic blood pressure, HDL cholesterol, HDL₂ cholesterol, LDL cholesterol, weight, and left ventricular mass. These values are expected if mating is random with respect to the causes of juvenile measures, gene action is additive, and family environment does not cause twin resemblance. These data also indicate that a high proportion of the variation in thiocyanate and HDL₃ cholesterol levels is attributable not to genetic effects but to environmental effects, such as passive smoking. The variation in 2,3-DPG levels appears balanced between genetic and environmental effects.

Discussion

We found alterations in systemic oxygen transport and lipoprotein composition in preadolescent children that were related to cigarette smoke exposure. Paternal smoking did not influence measures of passive smoke exposure, while maternal smoking affected children by providing passive smoke exposure in the home and possibly during gestation.

Our results indicate that, as in other tissue hypoxia states (anemias, chronic pulmonary disease, cyanotic heart disease, and high altitude), the body attempts to compensate for hypoxia by increasing the 2,3-DPG level in the blood to meet tissue oxygen requirements. A hypoxia-driven mechanism to trigger 2,3-DPG synthesis may be responsible for the increase in 2,3-DPG level in active smokers.^{22,23}

Erythrocytosis occurs frequently in adult active smokers. Hematocrit elevation in active smokers has been ascribed to long-term exposure of even low levels of carbon monoxide, which results in tissue hypoxia and leads to increased red cell mass.²⁴ Hematocrit values for the passive smoking and non-

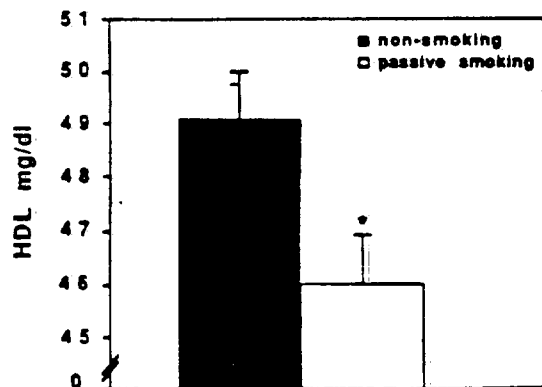


FIGURE 3. Bar graph of the comparison of total serum HDL cholesterol level in non-passive smoking ($n=106$) and passive smoking ($n=102$) children after adjusting for age, sex, height, and weight. Data represent group mean \pm SD. * $p < 0.05$. HDL, high density lipoprotein.

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passive smoking children in the present study were identical, though both groups were in the early stages of pubertal development. Steroid and adeno-hypophysial hormones, which positively influence erythropoiesis,²⁵ are low in preadolescent children and progressively increase during puberty. Longitudinal evaluation of passive smoking and non-passive smoking twins as they progress through puberty may detect differences in hematocrit and other oxygen transport variables, which may be related to the degree of passive cigarette smoke exposure.

The incidence of atherosclerotic coronary artery disease is strongly associated with increased levels of LDL cholesterol and decreased levels of HDL cholesterol, especially the HDL₂ cholesterol subfraction.²⁶⁻²⁷ Active cigarette smoking alters the total serum cholesterol concentration and lipoprotein composition, which directly increase the risk of coronary heart disease. In our population, children with a family history of premature cardiovascular death had lower levels of HDL₂ cholesterol than those without such a history.²¹

During puberty and early adolescence, levels of HDL and LDL cholesterol decrease in all children, but the decrease in HDL cholesterol is more pronounced in boys than in girls.²⁸ Since the girls in our study population were more sexually developed than the boys, we cannot exclude the possibility that the passive smoking girls were more advanced in pubertal development than their non-passive smoking counterparts, which could explain the observed differences in LDL cholesterol. HDL cholesterol levels fall during puberty in boys in association with increases in testosterone levels.²⁹ Passive cigarette smoking, by further diminishing the level of HDL₂ cholesterol in pubertal males, may be associated with accelerated atherosclerotic changes and an increased risk of coronary heart disease.

The passive smoking preadolescent boys demonstrated a tendency toward lower levels of the HDL₂ cholesterol subfraction, which was related to the number of cigarettes smoked daily by the parents of the boys. Because Bodurtha et al²¹ showed that coronary heart disease deaths occur more frequently in families with low levels of HDL₂ cholesterol, a lower HDL₂ cholesterol level in passive smoking boys likely represents an enhanced atherogenic risk factor for the subsequent development of atherosclerotic coronary heart disease.

Haffner et al³⁰ found a reduction in HDL₂ cholesterol subfraction levels with active cigarette smoking. These authors also found that alcohol consumption raised HDL₂ cholesterol levels. It appears therefore that HDL₂ cholesterol levels represent a reactive lipoprotein species that responds to specific environmental influences. Our data support this hypothesis by not only demonstrating lower HDL₂ cholesterol levels in passive smoking children but also the low heritability of HDL₂, implying high environmental variance.

Acknowledgments

We acknowledge the technical expertise of A. Cook, L. Stevenson, B. Toms, K. Vincent, C. Dickens, W. Wilson, M. Blanchard, and P. Winter.

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KEY WORDS • smoking, passive • high density lipoprotein cholesterol • atherosclerosis • cardiovascular disease, prevention

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Pomrehn, P., Hollarbush, J., Clarke, W. and Lauer, R., "Children's HDL-chol: The Effects of Tobacco; Smoking, Smokeless and Parental Smoking," Presented at the 30th Annual Conference on Cardiovascular Disease Epidemiology, Abstract, Circulation 81(2): 720, 1990.

This study evaluated HDL-cholesterol levels in a group of 6th and 7th grade children. Children whose parents smoked reportedly had lower HDL levels. Personal use of tobacco (smoking or chewing) by the children also was associated with lower HDL levels.

Comment

This report is available only as a meeting abstract, which provides few details on which to base an evaluation.

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Abstracts of the 30th Annual Conference on Cardiovascular Disease Epidemiology

March 29–31, 1990
San Diego Marriott Hotel and Marina
San Diego, California

Third-Day Program
Workshop on Obesity and Blood Pressure
March 31, 1990

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Children's HDL-cholesterol: The Effects of Tobacco Smoking, Smokeless and Parental Smoking

33

Paul Pomrehn, Janet Mollarbush, William Clarke, Ronald Lauer. University of Iowa, Iowa City, IA

Two projects, the Muscatine Ponderosity Study and the Prevention of Adolescent Smoking Project, provided an opportunity to relate tobacco exposure, particularly passive exposure due to parental smoking, and HDL-cholesterol levels. This report is based on the data gathered from the 451 students in grades 6 & 7 in the Muscatine, IA school system who participated in both surveys.

Children whose parents smoke daily had a lower mean HDL-cholesterol than those whose parents do not smoke; 49.0 mg/dl (n=209) vs. 51.7 mg/dl (n=242), $p < .01$. This association remained significant independent of body mass index, age and gender.

Regular tobacco use was reported by a small portion of students. Students smoking monthly or more have lower HDL-cholesterol levels (48.5 mg/dl (n=51) vs 50.7 mg/dl (n=399)). Boys who chew tobacco have lower HDL-cholesterol levels (47.1 mg/dl (n=27) vs 50.6 mg/dl (n=224), $p = .08$). In boys, but not girls, the combination of parental smoking and the child's chewing or smoking had the lowest HDL-cholesterol levels.

These results suggest that tobacco exposure by personal use of cigarettes or smokeless and passive exposure all contribute to lower HDL-cholesterol levels in children.

Change in Alcohol Consumption and Risk of All-Cause and Ischemic Heart Disease Mortality in the Alameda County Study

35

Nancy B. Lazarus, George A. Kaplan, Richard D. Cohen, Ding-Jen Leu. California Public Health Foundation, Berkeley, CA

Previous evidence suggests that those who abstain from alcohol consumption are at higher risk of ischemic heart disease (IHD) mortality. It remains controversial whether the increased risk is found among all abstainers or only those who recently quit drinking. Differentiating between long-term abstainers and more recent nondrinkers, the proportional hazards model was used to study the change in alcohol consumption from 1965 to 1974 and 10-year (1974-1984) all-cause and IHD mortality in 4,070 persons aged 35 and over. Women who were moderate drinkers who quit compared to light drinkers at both times are at increased risk of mortality from all-causes (RH = 6.56; 95% CI = 2.41 to 17.84) and from IHD (RH = 10.49; 95% CI = 2.50 to 44.01). This is true for men for all-cause mortality (RH = 1.78; 95% CI = 1.12 to 2.83) but not for IHD mortality (RH = 0.75; 95% CI = 0.31 to 1.83). For long-term abstainers compared to light drinkers, only men were at marginally increased risk and only for all-cause mortality (RH = 1.26; 95% CI = 0.91 to 1.75). Some of the increased risk associated with abstinence appears to be due to a higher risk among those who quit.

Mortality in Ex-drinkers

34

Arthur L. Klatsky, Mary Anne Armstrong, Gary D. Friedman. Kaiser Permanente Medical Center, Oakland, CA

Higher mortality in ex-drinkers (vs. lifelong abstainers) has usually been attributed to a higher prevalence of illness among ex-drinkers. Age-adjusted data for members of a prepaid health plan showed that 3810 ex-drinkers reported more illness than 15,510 abstainers (47.0% vs. 36.1%) but cardiovascular (CV) risk was similar (40.3% of ex-drinkers vs. 41.1% of abstainers). During follow-up from 1978-1985 (median follow-up = 5 years), 407 abstainers and 178 ex-drinkers died. Age-adjusted Cox regression analyses showed that, compared to lifelong abstainers, ex-drinkers had higher mortality from CV causes (relative risk [RR] = 1.5, 95% CI = 1.3-2.1, $p < 0.01$) and from non-CV causes (RR = 1.7, CI = 1.3-2.1, $p < 0.001$). Adjustment for additional covariates (sex, race, smoking, body mass index, marital status, education) reduced the mortality risk of ex-drinkers; RR for CV = 1.0, CI = 0.8-1.3 and RR for non-CV = 1.3, CI = 1.0-1.7, $p = 0.05$. Ex-drinkers who stopped for medical reasons had higher mortality from non-CV causes (RR = 1.5, CI = 1.1-2.1, $p = 0.01$), but not from CV causes (RR = 1.1, CI = 0.7-1.6). From these data, we conclude that higher non-CV mortality among ex-drinkers is due substantially to baseline illness, but higher CV mortality among ex-drinkers is due to confounding by other traits related to past alcohol use.

CHD Risk Associated with Regular and Acute Consumption of Alcohol

36

Rodney Jackson, Robert Scragg, Robert Beaglehole, University of Auckland, New Zealand

The association of regular and acute alcohol consumption with non-fatal myocardial infarction and coronary death was investigated in a case control study in New Zealand. A total of 1867 people aged 35-64 years without prior known coronary disease were included in the study. Interviews were conducted with 227 male and 77 female myocardial infarction cases identified in a community based MONICA register, and 525 male and 341 female controls, randomly selected from some population and group matched by age and sex. Data on coronary death cases (128 men and 30 women) identified in the MONICA register came from a close friend or relative. Similar information was obtained from a close friend or relative of 330 male and 214 female age and sex matched controls.

There was a strong, consistent inverse association between alcohol consumption and both fatal and non-fatal CHD risk in men and women. After controlling for possible confounding, people who drank alcohol more than once per month had a 30-60% reduction in CHD risk. Ex-drinkers had a reduced risk of non-fatal myocardial infarction but not of coronary death. Alcohol consumption was also associated with an acute reduction in CHD risk. Among people who drank at least once per month, CHD risk was halved during the 24 hours after a drinking episode.

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FELDMAN, J., SHENKDER, I.R., ETZEL, R.A., SPIERTO, F.W., LILIENTH, D.E., NUSSBAUM, M. AND JACOBSON, M.S., "PASSIVE SMOKING ALTERS LIPID PROFILES IN ADOLESCENTS," PEDIATRICS 88(2): 259-264, AUGUST 1991.

This study investigated the possible relationship between ETS exposure and blood lipid profiles in a group of New York suburban high school students who were undergoing pre-participation sports physicals. Exposure to ETS was estimated from the subjects' plasma cotinine levels. In addition, questionnaire data provided information concerning the subjects' cigarette smoking habits and regarding the cigarette smoking habits of their friends, parents and siblings.

ETS exposure, as inferred from plasma cotinine levels, was reported to be associated with an elevated ratio of total cholesterol to HDL cholesterol, and a lower HDL cholesterol level. In contrast to the data based on cotinine levels, the "association of lipid profiles with reported smoking habits of parents, siblings, and friends, was not statistically significant" (emphasis added; page 263, column 1). The authors nevertheless concluded:

These results suggest that passive smoking, like active smoking, leads to alterations in lipid profiles predictive of an increased risk of atherosclerosis. (p. 259, Abstract)

The authors acknowledged that, compared with other factors such as body mass index or triglyceride concentration, the impact of ETS exposure on lipoprotein profiles "was relatively small." (p. 263, col. 1) The authors also acknowledged that a number of

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confounding variables were not measured. In particular, they mentioned socioeconomic status and diet. Feldman, et al. nevertheless downplayed these factors because they considered their sample to be "relatively homogeneous."

We did not measure socioeconomic status of subjects or obtain detailed dietary histories and therefore could not control for these variables. It is possible that parents of lower economic status smoked more frequently and provided their children diets higher in cholesterol and saturated fats, resulting in a secondary association between serum cotinine concentration and lipid ratios. This seems an unlikely explanation, however, because the students came from a relatively homogeneous community. (p. 263, col. 1)

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Passive Smoking Alters Lipid Profiles in Adolescents

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ABSTRACT. Although cigarette smoking is associated with elevation of plasma lipid levels and changes in lipoprotein distribution, it is not known whether passive smoking is associated with an alteration in lipid profiles. The relation between plasma cotinine, a marker of exposure to tobacco smoke, and lipid profiles was studied in healthy adolescents from a suburban New York high school district who were undergoing preparticipation sports physicals. Forty-four percent of the adolescents reported that one or both parents currently smoked. Eleven percent of the adolescents had plasma cotinine concentrations ≥ 2.5 ng/mL, the level considered indicative of exposure. Adolescents with two smoking parents had significantly higher plasma cotinine concentrations after adjustment for other factors than adolescents whose parents did not smoke. Plasma cotinine concentration ≥ 2.5 ng/mL was associated with an 8.9% greater ratio of total cholesterol to high-density lipoprotein cholesterol ($P < .003$) and a 6.8% lower high-density lipoprotein cholesterol ($P < .03$). These results suggest that passive smoking, like active smoking, leads to alterations in lipid profiles predictive of an increased risk of atherosclerosis. *Pediatrics* 1991;88:259-264; *passive smoking, adolescents, cotinine, lipid profiles, cholesterol.*

ABBREVIATIONS. TOTAL-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; CV, coefficient of variation; BMI, body mass index; CI, confidence interval.

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Cigarette smoking is associated with elevation of plasma lipid levels and changes in lipoprotein distribution,¹ including an elevated ratio of total cholesterol (TOTAL-C) to high-density lipoprotein cholesterol (HDL-C).²⁻⁴ The TOTAL-C/HDL-C ratio is a powerful predictor of the risk of atherosclerotic cardiovascular disease and therefore its relationship to passive as well as active smoking has implications for pediatric atherosclerosis prevention.^{5,6}

The present study investigated the relationship of passive smoking to lipid profiles in healthy adolescents. Cotinine, a major metabolite of nicotine, was used as a marker of passive exposure to tobacco smoke.^{7,8} We hypothesized that passive exposure to environmental tobacco smoke as indicated by plasma cotinine concentration would be associated with an increase in the TOTAL-C/HDL-C ratio.

METHODS

As part of a required health risk assessment and preparticipation sports physical examination, non-fasting whole blood samples were obtained from 444 students attending suburban New York high schools in August 1987. All students trying out for an athletic team at the high schools took the physical. Students were asked to complete self-administered questionnaires about their cigarette smoking habits and diet. This questionnaire has previously been found to be reliable.⁹ In addition, students were interviewed by one of two authors (J.F., M.S.J.) regarding cigarette smoking habits of

their parents, siblings, and friends. To improve reliability, the first 10 interviews conducted by each interviewer were observed by the other interviewer. The procedures followed were approved by the Human Subjects Review Committee at Long Island Jewish Medical Center.

Passive exposure of tobacco smoke was grouped into five mutually exclusive categories based on the current cigarette smoking habits of the students' parents, siblings, and friends. The first three groups below were based solely on exposure to parental smoking without regard to sibs or friends. The five categories were as follows: (1) mother smoked but father did not, (2) father smoked but mother did not, (3) both parents smoked, (4) siblings and/or friends only smoked, and (5) no parents, siblings, or friends smoked. Exposure from any parents not currently living with the subject was excluded. Exposure from smoking friends was excluded if the student reported spending ≤ 2 hours per week in their company. Nonfasting plasma was collected by venipuncture from seated subjects, centrifuged, and frozen until analysis.

Cholesterol and triglycerides were assayed directly from 10 μ L of supernatant by a Kodak multilayer film method. High-density lipoprotein cholesterol was determined by drawing 0.5 mL of plasma into tubes containing 50 000 molecular weight dextran sulfate-magnesium reagent and centrifuging the mixture at $1500 \times g$ for 10 minutes to precipitate the very-low-density lipoprotein and low-density lipoprotein particles. The HDL-containing supernatant was then assayed directly for cholesterol using the Kodak multilayer film method. We analyzed 15 paired samples, both on a Kodak DT60 Analyzer and at Queens Hospital Center (New York) Arteriosclerosis Research Laboratory, which is a participant in the Centers for Disease Control/National Heart, Lung, and Blood Institute Lipid Standardization Program. Correlation coefficients were cholesterol = .99, triglycerides = .97, and HDL-C = .91.

Total cholesterol and HDL-C were measured in 11 batches. The coefficient of variation (CV) of total cholesterol by batch ranged from 0.16 to 0.20 whereas for HDL-C the CV ranged from 0.16 to 0.27. There were no significant differences in the average levels or the variation from the averages among the 11 batches in either males or females. Four hundred twenty-five of the students had sufficient plasma remaining for cotinine analysis. Plasma cotinine analysis was performed at the Division of Environmental Health Laboratory Sciences at the Centers for Disease Control using the radioimmunoassay previously described by Knight et al.¹⁰ The level of detection for cotinine in this

assay was 1.6 ng/mL. Cotinine and lipid concentrations were each determined without knowledge of reported exposure to tobacco smoke.

Notched box plots in the Figure were used to indicate the median cholesterol concentrations and the 95% confidence interval about the medians. If the notches in the boxes (ie, median $\pm 1.57 \times$ interquartile range/ \sqrt{n}) do not overlap, this can be regarded as strong evidence that the population medians differ.¹¹⁻¹³ Hatched areas in the Figure denote the area between the 75th and 25th percentile (ie, interquartile range).

Multiple linear analyses of covariance were performed using TOTAL-C, HDL-C, and ratio of TOTAL-C/HDL-C as outcomes. Covariates included age, race, sex, triglyceride concentration, and body mass index (BMI). Body mass index was calculated by dividing weight by the square of height. The predictor variables were plasma cotinine concentrations and self-reported passive tobacco smoke exposure. Inasmuch as the distributions of both cotinine and triglyceride concentrations were highly skewed, these data were logarithmically transformed. This transformation of the serum cotinine levels was also useful in testing for differences among the exposure groups, inasmuch as the similarity of the CV of cotinine among the exposure categories (from 1.6 to 2.4) suggested proportional effects.¹⁴ We report both the arithmetic and geometric means of cotinine. The constant 0.05 was added to all cotinine concentrations to avoid the logarithm of zero which is undefined. In addition,

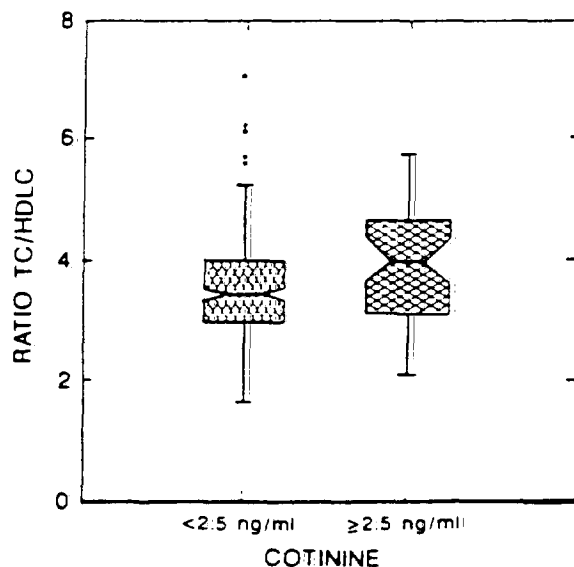


Figure. Lipid ratio in passive smoke-exposed and nonexposed adolescents. TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; *, outlier values.

plasma cotinine concentrations were categorized as <2.5 ng/mL or ≥ 2.5 ng/mL to indicate exposure based on previous work.¹⁵ Interactions between the covariates and the predictor variables were examined and none was significant. The adequacy of the assumptions underlying the various models was assessed by examining various residual plots.¹¹ Reanalysis omitting highly leveraged cases (ie, dropping cases with a much greater than average impact on results) did not change any conclusions. The actual computations were performed using Systat.¹⁶

Self-reported smokers ($n = 7$) were excluded. To reduce the possibility of including current smokers who did not report accurately, students with plasma cotinine concentrations of more than 25 ng/mL ($n = 12$) and nonresponders to the smoking question ($n = 2$) were also excluded.⁷ In addition, we excluded 7 adolescents on cholesterol-lowering diets and 6 nonresponders to the diet question. The study sample therefore consisted of 391 adolescents. The analyses in Tables 3 and 4 were also done excluding 5 adolescents with serum cotinine values of 11 to 25 to further reduce the possibility of misclassification of active smokers. The results were almost identical and therefore are not shown.

RESULTS

The sample included 274 boys (69.7%) and 117 girls (30.3%). Two hundred seventy-eight (71.1%) were white, 52 (13.2%) were black, 20 (5.1%) were other races, and 41 (10.5%) did not indicate their race. The mean age was 14.8 ± 1.6 years; 34.3% of the adolescents reported no smokers among their parents, siblings, or friends; 15.1% reported that mother smoked but father did not; 17.4% reported that father smoked but mother did not; 11.5% reported that both parents smoked; and 21.7% reported that siblings and/or friends only smoked. The arithmetic mean cotinine concentration was 1.39 ng/mL ($SD = 4.70$), which was not significantly different from the level of detection of the assay. Eleven percent ($n = 44$) of the adolescents had plasma cotinine concentrations ≥ 2.5 ng/mL, 89% ($n = 347$) had plasma cotinine concentrations <2.5 ng/mL. Both the geometric and arithmetic mean plasma cotinine concentrations were significantly higher among adolescents who reported that one or both parents smoked; the highest level was found among adolescents with two smoking parents (Table 1). Table 2 shows average levels of the ratio of TOTAL-C/HDL-C by reported exposure and category of serum cotinine concentration. The TOTAL-C/HDL-C ratio was always higher in children whose serum cotinine level was ≥ 2.5 ng/mL irre-

spective of reported exposure. Despite the statistically significant association between reported exposure and serum cotinine concentration, it was apparent that there was considerable misclassification of exposure based on self-report. Fewer than 20% of the students in any reported exposure category were classified as exposed based on serum cotinine levels greater than or equal to 2.5 ng/mL (Table 2).

Mean TOTAL-C concentration was 154 mg/dL ($SD = 27.2$), mean HDL-C concentration was 44.6 mg/dL ($SD = 10.0$), and mean TOTAL-C/HDL-C ratio was 3.58 ($SD = 1.86$). The Figure shows notched box plots for the ratio of TOTAL-C/HDL-C by cotinine group with 95% confidence intervals about the medians. The asterisks in the Figure indicate observations that fall outside the 95% range of individual values. The median TOTAL-C/HDL-C ratio for the 44 adolescents with cotinine concentrations ≥ 2.5 ng/mL was significantly higher than that for the 347 adolescents with cotinine concentrations <2.5 ng/mL ($P < .002$). This was not true for HDL-C concentrations until covariates were taken into account as described later.

In the analysis of covariance model with outcome equal to the ratio of TOTAL-C/HDL-C, the independent variables BMI, log triglyceride level, and log cotinine level were all significantly associated with the ratio (not shown). Together the variables accounted for 28% of the variation in the ratio of TOTAL-C/HDL-C, with triglyceride concentration and BMI accounting for 97% of that amount. Results of analysis with cotinine grouped into two categories are shown in Table 3. Cotinine level was significantly associated with the ratio of TOTAL-C/HDL-C ($P < .003$). [The regression equation was $\text{ratio} = -.60 + .038 (\text{BMI}) + .771 \ln (\text{triglyceride}) - .324$ (if cotinine level <2.5 ng/mL) + $.379$ (if white).] For the group with cotinine levels ≥ 2.5 ng/mL, the ratio of TOTAL-C/HDL-C on average was .324 or 8.9% (95% confidence interval) [CI 6.9% to 11.0%] higher than if the cotinine level was <2.5 ng/mL. Cotinine level was significantly associated with lower HDL-C concentration ($P < .03$) (Table 4). [$\text{HDL-C} = 77.8 - 5.4 \ln (\text{triglyceride}) - 0.48 (\text{BMI}) + 3.0$ (if cotinine level <2.5 ng/mL) - 2.56 (if male).] The HDL-C level in adolescents with plasma cotinine concentration ≥ 2.5 ng/mL was 3.0 mg/dL or 6.8% (95% CI 4.6% to 8.9%) lower than in those with plasma cotinine concentration <2.5 ng/mL after adjustment for other factors.

The association of serum cotinine concentration with the ratio of TOTAL-C/HDL-C was examined separately for whites with similar results ($P = .001$), as well as for boys ($P = .014$) and girls ($P = .001$).

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TABLE 1. Arithmetic and Geometric Mean Levels and 95% Confidence Intervals (CI) for Serum Cotinine Levels by Reported Exposure

Reported Exposure	n	Arithmetic Mean (95% CI)	Geometric Mean (95% CI)
None	134	0.55 (0.40-0.69)	0.07 (0.04-0.11)
Friends/sibs only	87	1.35 (0.66-2.03)	0.07 (0.04-0.14)
Mother, not father	59	1.06 (0.49-1.62)	0.13 (0.07-0.26)
Father, not mother	66	1.39 (0.75-2.02)	0.21 (0.11-0.39)
Both mother and father	45	2.15 (0.81-3.49)	0.35 (0.17-0.74)
F ratio 4.386 df		3.65	4.48
P value		0.006	0.001

TABLE 2. Ratio of Total Cholesterol to High-Density Lipoprotein Cholesterol by Serum Cotinine Group and Reported Exposure

Reported Exposure	Serum Cotinine Concentration					
	<2.5 ng/mL			≥2.5 ng/mL		
	n	Ratio	SD	n	Ratio	SD
None	124	3.47	0.87	10	3.77	0.76
Friends/sibs only	71	3.55	0.90	16	3.70	1.13
Mother, not father	49	3.34	0.55	10	4.06	1.02
Father, not mother	33	3.64	0.78	13	4.22	1.04
Both mother and father	37	3.68	0.85	8	3.91	1.02

TABLE 3. Multiple Regression Analysis of Ratio of Total Cholesterol to High-Density Lipoprotein Cholesterol by Plasma Cotinine Concentration, Grouped, Adjusted for Several Covariates*

Source of Variation	SS	df	F Ratio	P Value
Race	1.72	2	1.81	.165
Body mass index	6.64	1	13.99	.000
Cotinine grouped: <2.5 ng/mL vs ≥2.5 ng/mL	4.27	1	9.01	.003
Log triglyceride	44.00	1	92.79	.000
Error	160.29	338		

* SS = sum of squares; N = 344; $r = .54$. Forty-seven patients with missing data on any of the above variables are excluded.

TABLE 4. Multiple Regression Analysis of High-Density Lipoprotein Cholesterol by Grouped Plasma Cotinine Levels Adjusted for Several Covariates*

Source of Variation	SS	df	F Ratio	P Value
Sex	515.20	1	5.77	.017
Log triglyceride	2346.87	1	26.27	.000
Body mass index	1152.40	1	12.90	.000
Cotinine grouped: <2.5 ng/mL or ≥2.5 ng/mL	427.50	1	4.79	.030
Error	34041.56	381		

* N = 386; $r = .35$. Five patients with data missing on any of these variables are excluded.

The relationship between reported smoking habits of parents, siblings, and friends and the ratio of TOTAL-C/HDL-C was not statistically significant ($P = .18$). There was a significant difference in the ratio of TOTAL-C/HDL-C of adolescents whose fathers smoked compared with others ($P \leq .04$). When adjusted for multiple comparison bias, this finding was no longer statistically significant. There was no difference in the ratio of TOTAL-C/

HDL-C of adolescents whose mothers smoked compared with others.

DISCUSSION

In this sample, passive exposure to tobacco smoke as indicated by plasma cotinine concentration was associated with a higher ratio of TOTAL-C/HDL-C and with a lower HDL-C concentration.

When other factors were adjusted, passive exposure to tobacco smoke was associated with an increased ratio of TOTAL-C/HDL-C and decreased HDL-C concentration of between 7% and 9%. However, compared with other factors such as BMI or triglyceride concentration, the impact of passive smoking on the ratio of TOTAL-C/HDL-C was relatively small.

We did not measure socioeconomic status of subjects or obtain detailed dietary histories and therefore could not control for these variables. It is possible that parents of lower economic status smoked more frequently and provided their children diets higher in cholesterol and saturated fats, resulting in a secondary association between serum cotinine concentration and lipid ratios. This seems an unlikely explanation, however, because the students came from a relatively homogeneous community.

The association of lipid profiles with reported smoking habits of parents, siblings, and friends was not statistically significant. There was an association for adolescents whose fathers smoked compared with others. But there was no association with mothers' smoking. We did not predict this pattern initially and the observation is inconsistent with other reports, which have found a stronger association with mothers' smoking.¹⁶ The most likely explanation for this pattern is a spurious association. Parenthetically, this pattern also diminishes the likelihood that the observed association between the lipid ratio and cotinine concentration was due to smoking mothers' providing a more atherogenic diet. The association of passive exposure to tobacco smoke with reduced HDL-C and elevated ratio of TOTAL-C/HDL-C is biologically plausible, inasmuch as several investigators have found that cigarette smoking results in a lowering of HDL-C.^{1,5,18-20} In one longitudinal study of 36 female volunteers, investigators found that HDL-C levels fluctuated with smoking status, increasing when smoking ceased and decreasing when smoking resumed.²¹ In another study, investigators reported a dose-response relationship between smoking and ratio of TOTAL-C/HDL-C.⁴ The age- and weight-adjusted ratio of TOTAL-C/HDL-C among 233 randomly selected families was 13% higher for smokers than for nonsmokers, about 1.5 times that seen in this study.

Several investigators have found suggestive evidence of an increased risk of coronary heart disease mortality among adults passively exposed to tobacco smoke. Helsing et al.²² found that death rates from atherosclerotic heart disease were 24% to 31% higher for nonsmokers living with smokers compared with those living with nonsmokers. In a study

of nonsmoking women 50 to 79 years old in southern California, those whose husbands smoked had a 10-year mortality from ischemic heart disease that was 2.7 times higher than those whose husbands never smoked ($P \leq .10$).^{23,24} In the Multiple Risk Factor Intervention Trial, the effect of exposure to tobacco smoke was assessed among 1245 married men aged 35 to 57 years.²⁵ The relative risk for nonsmoking men with smoking wives compared with those with nonsmoking wives was 2.1 for coronary heart disease death ($P = .19$); and 1.48 for fatal or nonfatal coronary heart disease events ($P = .13$).

A recent study in 216 families of preadolescent children from the Medical College of Virginia twin study found that children in the 105 families of smoking parents had significantly lower HDL-C and higher whole blood 2,3-d-phosphoglycerate levels than children in the 111 nonsmoking families.²⁶ The authors concluded that children with long-term exposure to passive smoke may be at elevated risk for the development of premature coronary heart disease.

The effect of tobacco on lipid levels provides one plausible mechanism (among others such as platelet aggregation, vasoactivity, and compromised oxygen transport) for the well-established elevation of coronary heart disease risk among smokers and suggests a mechanism for the possible increased coronary heart disease risk in passive smokers.

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PATIENTS' GRADES HELP TO SET PAY FOR HEALTH-PLAN DOCTORS

A growing number of large health-care plans are asking patients to grade their doctors: How long are they kept waiting in the office? Can the doctor be reached at night and on weekends? Does the doctor listen as patients describe symptoms? How well is a treatment explained?

Some health maintenance organizations, or H.M.O.'s, use the grades as one criterion in paying the doctors. Not surprisingly, many doctors think this is a bad idea.

At least 34 million Americans are enrolled in H.M.O. plans, and more than 2.9 million are in plans that use patient evaluations to help determine doctors' bonuses. The number of such plans is steadily increasing.

Freudenheim M. Patients' grades help to set pay for health-plan doctors. *The New York Times.* May 26, 1990.

NOTED BY J.F.L., MD

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WHIG, J., SINGH, C.B., SONI, G.L. AND BANSAL, A.K., "SERUM LIPIDS & LIPOPROTEIN PROFILES OF CIGARETTE SMOKERS & PASSIVE SMOKERS," INDIAN J MED RES B(96): 282-287, 1992.

This study from India presented data on lipoprotein profiles in relation to smoking status and history of exposure to ETS. "Passive smokers" were defined as those nonsmokers "who were chronically exposed to smoke of at least 20 cigarettes a day, in their homes and/or in work places in closed environment of room(s)/office(s)." The method of obtaining information on ETS exposure was not described. The authors reported that both active smoking and ETS exposure altered lipoprotein profiles in a direction that would increase heart disease risk.

In conclusion, our findings suggest that smoking alters the serum lipid and lipoproteins and these changes become more marked with duration and amount of smoking. The passive smokers also show relatively less altered lipid and lipoproteins, in a trend similar to that of smokers. The alteration in the individual value of lipids and lipoproteins is not significant in case of passive smokers but the results are significant only in case of ratios of HDL_C/T_C and HDL_C/LDL_C . As decrease in this ratio is responsible for the development of atherosclerosis, the results indicate that even the passive smokers are at a relatively higher risk of developing coronary heart disease. (p. 286)

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Serum lipids & lipoprotein profiles of cigarette smokers & passive smokers

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Serum lipids and lipoproteins of 50 active and passive smokers were compared with levels in 25 control subjects. Active smoking resulted in an increase in total cholesterol (T_c) and triglycerides (T_g) as compared to control group. The passive smokers also showed relatively higher levels but the effect was not significant. Active smoking raised the low density lipoprotein cholesterol (LDL_c) and very low density lipoprotein cholesterol ($VLDL_c$) levels whereas high density lipoprotein cholesterol (HDL_c) content was lowered, thus resulting in decreased ratios of HDL_c/T_c and HDL_c/LDL_c . The passive smokers also showed slightly higher levels of LDL_c and $VLDL_c$ but lower levels of HDL_c and a lower HDL_c/LDL_c ratio. Our findings suggest that smoking alters the serum lipids and lipoproteins and these changes are related to the duration and amount of smoking.

Large prospective epidemiological studies have shown strong association between cigarette smoking and several diseases. The potential of developing coronary artery disease in male cigarette smokers is approximately 2.14 times greater than in non-smokers¹. The risk of infarction for both men and women is correlated with the number of cigarettes smoked daily². Association of cigarette smoking, serum lipoproteins and coronary artery disease has been reported by several workers^{3,4}.

Various reports suggest that involuntary inhalation of cigarette smoke by non-smokers causes disease, most notably lung disease^{5,6}. The ubiquitousness of tobacco smoke in homes, work places and public areas makes exposure to environmental tobacco smoke unavoidable^{7,8}.

Asymptomatic non-smokers who are chronically exposed to smoke contaminated air may develop small airway dysfunction^{9,10}. Several studies suggest that passive smoking increases the risk for lung cancer⁶ and aggravates angina pectoris¹¹.

Very little attention has been paid to the effect of passive smoking on serum lipids and lipoproteins. In view of the fact that large population in India is exposed to passive smoking, the present study has been undertaken to know the effect of passive smoking on serum lipids and lipoproteins compared to that in chronic smokers and control subjects.

Material & Methods

A total of 75 subjects of middle income group known to perform moderate physical activity were

included in the present study. Twenty five males who smoked more than 15 cigarettes a day for more than 5 consecutive years were taken as smokers, 25 non-smokers who were chronically exposed to smoke of at least 20 cigarettes a day, in their homes and/or in work places in closed environment of room (s)/ office (s) were taken as passive smokers. Similarly, 25 male non-smokers matched for age and physical activity were taken as control; these individuals lived with strict non-smokers at home and also in their work place.

Subjects suffering from diseases which are known to alter the lipid profile such as diabetes mellitus, uremia, nephrotic syndrome, hypothyroidism, hyperthyroidism and acromegaly, were excluded from the study. Alcoholics and subjects on steroids were also excluded from the study.

Ten ml of blood sample was collected after an overnight fast from each subject. The serum was separated by centrifugation at 3000 rpm for 10 min and was used for lipid and lipoprotein analysis. Total lipids were extracted from the serum¹² and serum total cholesterol (T_c)¹³, serum triglycerides (T_g)¹⁴ in the extracted lipids, HDL_c¹⁵, LDL_c and VLDL_c¹⁶ were estimated. Student's t -test was used for analysis of the data.

Results

Table I shows the comparison of T_c and T_g of smokers and passive smokers with that of control subjects. Significantly higher levels of T_c ($P < 0.05$)

and T_g ($P < 0.01$) were observed in smokers whereas the passive smokers showed marginally higher levels but the values were statistically insignificant when compared to controls. The active smokers had significantly higher levels of LDL_c ($P < 0.01$) and VLDL_c ($P < 0.05$) than controls, whereas these levels of passive smokers showed no significant difference (Table II). The levels of HDL_c in both groups were not significantly different when compared with control. The ratios of HDL_c/ T_c and HDL_c/LDL_c of smokers were significantly lower ($P < 0.01$) as compared to control group. Passive smokers, however, showed significantly lower ($P < 0.05$) ratio of HDL_c/LDL_c only (Table III).

Table IV shows the T_c and T_g of moderate and heavy smokers of different durations. Moderate smokers (smoking 15 to 20 cigarettes/day) who were smoking for more than 15 yr and heavy smokers (smoking more than 20 cigarettes/day) irrespective of the duration showed significantly higher levels of T_c ($P < 0.05$) and T_g ($P < 0.01$) when compared to controls. LDL_c of moderate and heavy smokers were also significantly higher ($P < 0.05$) irrespective of duration of smoking, whereas no significant differences were observed in HDL_c of both groups as compared to control group (Table V). The levels of VLDL_c were also significantly higher in moderate smokers who smoked for more than 15 yr and heavy smokers. Irrespective of the duration of smoking both heavy and moderate smokers had significantly

Table I. Comparison of total cholesterol (T_c) and triglycerides (T_g) of smokers and passive smokers with non-smoker controls

	T_c (mg/dl)		T_g (mg/dl)	
	Range	Mean \pm SE	Range	Mean \pm SE
Control (n = 25)	140-270	197.72 \pm 7.04	80-126	100.16 \pm 2.46
Smokers (n = 25)	180-300	233.28 \pm 5.83**	96-166	131.32 \pm 3.77*
Passive smokers (n = 25)	146-266	202.00 \pm 4.62	80-138	106.00 \pm 2.76

P values. * < 0.01 ; ** < 0.05 , as compared to controls

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Table II. Comparison of cholesterol of lipoprotein fractions in smokers and passive smokers with controls

	HDL _c (mg/dl)		LDL _c (mg/dl)		VLDL _c (mg/dl)	
	Range	Mean \pm SE	Range	Mean \pm SE	Range	Mean \pm SE
Control (n = 25)	38-74	58.28 \pm 1.80	75-174	117.68 \pm 5.68	17-29	21.76 \pm 0.69
Smokers (n = 25)	40-76	52.88 \pm 1.68	116-221	153.52 \pm 4.96*	18-37	26.88 \pm 1.06**
Passive smokers (n = 25)	40-73	55.24 \pm 1.72	83-170	123.72 \pm 3.81	16-32	22.80 \pm 0.72

P values, * <0.01 ; ** <0.05 , as compared to controlsTable III. Ratio of HDL_c/T_c and HDL_c/LDL_c of smokers and passive smokers compared with controls

	HDL _c /T _c		HDL _c /LDL _c	
	Range	Mean \pm SE	Range	Mean \pm SE
Control (n = 25)	0.25-0.36	0.30 \pm 0.006	0.37-0.68	0.51 \pm 0.016
Smokers (n = 25)	0.17-0.28	0.23 \pm 0.006*	0.24-0.47	0.35 \pm 0.012*
Passive smokers (n = 25)	0.18-0.38	0.28 \pm 0.008	0.24-0.65	0.45 \pm 0.016**

P values, * <0.01 ; ** <0.05 , as compared to controlsTable IV. T_c and T_g of moderate and heavy smokers of different durations

Duration yr	T _c (mg/dl)		T _g (mg/dl)	
	Range	Mean \pm SE	Range	Mean \pm SE
Control (n = 25)	140-270	197.72 \pm 7.04	80-120	100.16 \pm 2.46
Moderate smokers (15-20 cig./day)	< 15 (n = 8)	180-246	96-156	117.75 \pm 6.82
	> 15 (n = 6)	190-300	120-166	136.67 \pm 6.54*
Heavy smokers (< 20 cig. day)	< 15 (n = 6)	210-266	118-155	137.50 \pm 6.39*
	> 15 (n = 5)	217-300	110-156	139.20 \pm 7.81*

P values, * <0.01 ; ** <0.05 , as compared to controls

higher ($P < 0.01$) HDL_c/LDL_c and HDL_c/T_c ratios as compared to controls (Table VI).

Discussion

There is increasing epidemiological evidence on

the association of cigarette smoking, serum lipoproteins and cardiovascular diseases¹⁷. In the present study, the serum lipids and lipoproteins of cigarette smokers and passive smokers have been compared with strict non-smokers. Comparison of

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Table V. Comparison of cholesterol of lipoprotein fractions of moderate and heavy smokers of different duration with controls

	Duration, yr	HDL _c (mg/dl)		LDL _c (mg/dl)		VLDL _c (mg/dl)	
		Range	Mean \pm SE	Range	Mean \pm SE	Range	Mean \pm SE
Control (n = 25)		38-74	58.28 \pm 1.80	75-174	117.68 \pm 5.68	17-29	21.76 \pm 0.69
Moderate smokers (15-20 cig./day)	< 15 (n = 8)	42-64	51.00 \pm 2.58	120-177	141.13 \pm 6.19**	18-37	23.75 \pm 2.08
	> 15 (n = 6)	48-66	59.33 \pm 4.37	116-201	157.33 \pm 12.94**	23-33	26.83 \pm 1.35**
Heavy smokers (< 20 cig./day)	< 15 (n = 6)	44-58	51.50 \pm 2.39	134-180	151.83 \pm 6.29**	22-37	27.50 \pm 2.17**
	> 15 (n = 5)	40-60	49.80 \pm 3.41	146-221	170.80 \pm 13.33**	27-36	31.20 \pm 1.71*

P values, * < 0.01; ** < 0.05, as compared to controls

Table VI. Ratio of HDL_c/T_c and HDL_c/LDL_c of moderate and heavy smokers of different durations compared with control

	Duration, yr	HDL _c /T _c		HDL _c /LDL _c	
		Range	Mean \pm SE	Range	Mean \pm SE
Control (n = 25)		0.25-0.36	0.30 \pm 0.006	0.37-0.68	0.51 \pm 0.016
Moderate smokers (15-20 cig./day)	< 15 (n = 8)	0.18-0.28	0.24 \pm 0.014*	0.25-0.44	0.37 \pm 0.021*
	> 15 (n = 6)	0.21-0.28	0.24 \pm 0.012*	0.30-0.47	0.38 \pm 0.024*
Heavy smokers (> 20 cig./day)	< 15 (n = 6)	0.20-0.25	0.22 \pm 0.008*	0.29-0.39	0.34 \pm 0.040*
	> 15 (n = 5)	0.17-0.24	0.20 \pm 0.013*	0.24-0.38	0.30 \pm 0.027*

P values, * < 0.01, as compared to controls

T_c and T_g levels indicated that cigarette smoking raised T_c and T_g levels. These findings are in accordance with the observations of other workers¹⁸⁻²¹, but contrary to a few who did not observe such an effect²². Since higher T_c and T_g levels are known to be responsible for the development of atherosclerosis²³, it indicates that active cigarette smoking can be a major risk factor for coronary artery disease.

Our findings of raised T_c and T_g levels in moderate smokers who had smoked for more than 15 yr and in heavy smokers (i.e., respective of the duration of smoking) are in agreement with the reports of a number of other workers from different parts of the world^{18, 19, 24}. However, a

few workers did not observe any change in T_c levels in smokers^{20, 25}.

The levels of LDL_c and VLDL_c were higher in heavy smokers or those who had smoked for longer duration. The differences observed in serum lipoproteins between smokers and non-smokers were in accordance with the observations of other workers^{19, 21, 24, 26}. However, Howell²⁷ and Young²⁸ did not observe any differences. The HDL_c of smokers was lower than that of control and passive smokers. Recently, Rastogi *et al.*²⁴ have also reported a similar effect on HDL_c in heavy smokers or those who were smoking for longer duration.

The comparison of the ratios HDL_c/T_c and

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HDL/LDL indicated that smokers had a significantly lower value. Investigators from the Framingham Heart Study²⁸ have proposed that these ratios may be better predictors of coronary risk than T_c or any of the lipoprotein cholesterol levels alone. Lowering of this ratio is known to increase the risk of development of cardiovascular disease. It is thus clear that smoking is a great hazard with respect to cardiovascular diseases. Since the ratio of HDL/LDL is also significantly lower amongst passive smokers, it indicates that not only active smokers but also subjects who are in contact with active smokers are at a relatively higher risk of developing atherosclerosis. The lower degree of risk amongst passive smokers compared to that amongst active smokers could be due to the filtration of smoke in the lungs of the smokers. Some of the components like nicotine and tar are deposited in the lungs of active smokers and therefore the passive smokers are exposed to a lower density of harmful components. Swendsen *et al*²⁹ conducted the multiple risk factor intervention trial to study the effects of passive smoking and the data from their study suggested that passive exposure to cigarette smoke may have a deleterious impact on the health of non-smokers and the non-smokers may be at an increased risk of death through passive exposure to cigarette smoke. Our findings also support this, as the levels of serum lipids and lipoproteins were altered in passive smokers in such a manner that it may have a deleterious effect on cardiovascular system.

The full impact of smoking on cardiovascular disease may not be revealed by available epidemiological surveys as risk ratios derived from these surveys do not necessarily reveal all of the cardiovascular consequences of smoking. It has been demonstrated that heavy smokers are at a higher risk than light smokers³.

In conclusion, our findings suggest that smoking alters the serum lipid and lipoproteins and these changes become more marked with duration and amount of smoking. The passive smokers also show relatively less altered lipid and lipoproteins, in a trend similar to that of smokers. The alteration in the individual value of lipids and

lipoproteins is not significant in case of passive smokers but the results are significant only in case of ratios of HDL/ T_c and HDL/LDL. As decrease in this ratio is responsible for the development of atherosclerosis, the results indicate that even the passive smokers are at a relatively higher risk of developing coronary heart disease.

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WHITE, J.R., CRIQUI, M., KULIK, J.A., FROEB, H.F. AND SINSHEIMER, P.J., "SERUM LIPOPROTEINS IN NONSMOKERS CHRONICALLY EXPOSED TO TOBACCO SMOKE IN THE WORKPLACE," ABSTRACT # 383, 8TH WORLD CONFERENCE ON TOBACCO OR HEALTH: BUILDING A TOBACCO-FREE WORLD, MARCH 30-APRIL 3, 1992, BUENOS AIRES, ARGENTINA

At the Eighth World Conference on Tobacco or Health in Buenos Aires, Argentina (March 30-April 3, 1992), a study was reported by James R. White, et al. (University of California-San Diego) which claimed that workplace ETS exposure adversely affected cholesterol profiles. At the time of the conference, the White, et al. study was the fourth publication since 1990 to address the general issue of a possible association of ETS exposure with changes in cholesterol levels. (See Note 1) However, it is the first to report data on cholesterol levels and ETS exposure in an adult population and to specifically address workplace ETS exposure.

White, et al. evaluated cholesterol and cholesterol fraction levels in nonsmoking workers. Carbon monoxide levels were used "as an index of cigarette smoke in the work place." [sic: the conference abstract refers, presumably reflecting a typographical error, to measurement of carbon dioxide.]

Both male and female workers classified as exposed to ETS were reported to have statistically significant decreases in high density lipoprotein (HDL) cholesterol (i.e., the "good" cholesterol) and elevated ratios of total cholesterol to HDL. In addition, females exposed to ETS were reported to have significant elevations in low density lipoprotein (LDL) cholesterol (i.e., the "bad" cholesterol).

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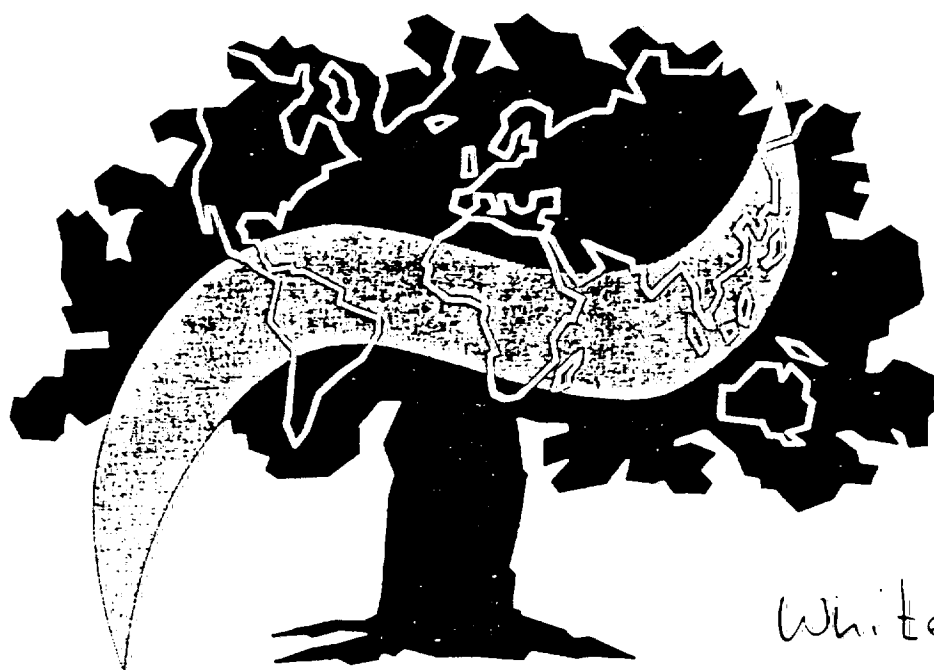
The authors concluded:

Nonsmoking workers are at increased risk of developing coronary heart disease resulting from exposure to second-hand tobacco smoke.

Note 1. The other three studies are as follows. (1) Based on a study of 11-year old children, Moskowitz, et al. (Circulation 81: 586-592, 1990) reported that ETS exposure, i.e., having at least one parent who smoked, was associated with reductions in HDL levels. (2) Similar data were reported in an abstract by Pomrehn, et al. (Circulation 81: 720, 1990), based on a study of sixth and seventh grade children. (3) Feldman, et al. (Pediatrics 88: 259-264, 1991) reported a study of cholesterol profiles in nonsmoking high school students, using plasma cotinine as an estimate of ETS exposure. Plasma cotinine levels were reportedly associated with a reduction in HDL cholesterol, as well as an elevation in the ratio of total cholesterol to HDL cholesterol.

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White, J. S.



8th WORLD
CONFERENCE
on TOBACCO
OR HEALTH

Building a Tobacco-Free World

March 30 - April 3, 1992
Buenos Aires - Argentina

ABSTRACTS, POSTERS and VIDEOS

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SERUM LIPOPROTEINS IN NONSMOKERS CHRONICALLY EXPOSED TO TOBACCO SMOKE IN THE WORKPLACE

James R. White, Ph.D., Michael Criqui, M.D., MPH, James A. Kulik, Ph.D.,
Herman F. Froeb, M.D., Peter J. Sinsheimer, MPH.

Department of Physical Education,
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We evaluated Carbon Dioxide (CO) levels as an index of cigarette smoke in the work place and determined lipoprotein levels in 40 passive smokers (nonsmokers chronically exposed to tobacco smoke in the work place) and 40 control subjects (nonsmokers not exposed to tobacco smoke in the work place) matched for age and gender.

Passive smokers experienced greater CO levels during the workday. Passive smokers, regardless of gender, had both significantly depressed high-density lipoprotein (HDL) levels and a significantly elevated total cholesterol to HDL (TC/HDL) ratio compared to nonsmokers. Additionally, female passive smokers had significantly elevated low-density lipoprotein (LDL) levels than female nonsmokers. Adjusting for the potential covariates of exercise, alcohol consumption, dietary fat intake, and percent body fat did not effect the significance of the results. Nonsmoking workers are at increased risk of developing coronary heart disease resulting from exposure to second-hand tobacco smoke.

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CIGARETTE ADVERTISING AND IMAGERY IN BRITISH WOMEN'S MAGAZINES

Amanda Amos, Bobbie Jacobson, Patti White*

*Health Education Authority, Hamilton House, Mabledon Place, London WC1H 9TX, UNITED KINGDOM

Women's magazines are read by about half of British women from all age and social groups. After a 1985 survey of cigarette advertising policies in these magazines showed that advertisements were being targeted at teens and young women, the British government made a voluntary agreement with the tobacco industry that limited the placement of advertisements in these publications. In 1989, the survey was repeated among 86 magazines. Data were obtained on cigarette advertising policies and revenues, general advertising policies, use of smoking imagery in editorial pages and editorial coverage of smoking and health. It was concluded that the government's voluntary agreement with the tobacco companies had failed to achieve the objective of protecting young women from exposure to cigarette advertising in women's magazines. This paper will report on the results of the survey.

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HOWARD, G., SZKLO, M., EVANS, G., TELL, G., ECKFELDT, J., HEISS, G. AND THE ARIC INVESTIGATORS, "THE ASSOCIATION BETWEEN CAROTID ARTERIAL WALL THICKNESS AND ACTIVE AND PASSIVE CIGARETTE SMOKING," ARTERIOSCLEROSIS AND THROMBOSIS 11(5): 1432A, 1991.

HOWARD, G., SZKLO, M., EVANS, G., TELL, G., ECKFELDT, J. AND HEISS, G., "PASSIVE SMOKING AND CAROTID ARTERY WALL THICKNESS: THE ARIC STUDY," CIRCULATION 85(2): 3, 1992.

An abstract, from the Bowman Gray School of Medicine (Winston Salem, North Carolina), based on a presentation at a November 1991 American Heart Association meeting, reported that ETS exposure was associated with thickness of the walls of the carotid arteries. (Howard, et al., 1991) The importance of carotid artery thickness is that it may be an indication of the severity of atherosclerotic involvement. Atherosclerosis of the carotid arteries is believed to underlie certain forms of stroke. These data were updated in a presentation at a March 1992 cardiovascular disease epidemiology conference, the abstract from which included information on some additional subjects, but otherwise reported similar results. (Howard, et al., 1992)

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gene expression in cynomolgus monkeys, that IL-1 β is expressed in both early and advanced stages of diet-induced atherosclerosis, as well as in monkey monocytes/macrophages, and suggest that this model can be employed to study the role of IL-1 β in atherogenesis.

Extensive Oxidation of LDL Induces Particle Aggregation and Altered Macrophage Recognition

Henry F. Hoff, Todd E. Whitaker, and June O'Neill

Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio

Although studies have reported structural and functional changes in LDL following oxidation (ox-), none have described such changes with increasing degrees of ox. We describe time-dependent changes in chemical and structural composition of ox-LDL and how they affect macrophage interaction. LDL (500 μ g/ml) was incubated with 10 μ M Cu²⁺ at 20°C for up to 25 hr. Time-dependent increases in conjugated dienes, fluorescence (360ex/430em), and particle aggregation (aggr.) were found, the latter increasing with LDL concentration used. Similar degrees of LDL ox. gave fragments of apo B of the same size. Extensive LDL ox. induced aggr. of apo B, possibly caused by covalent cross-linking of apo B, since apo B from aggr. ox-LDL but not from vortex-aggr. LDL was insoluble in SDS. Mildly ox-LDL eg. 8 hr in Cu²⁺ (unaggr.) and the soluble portion of extensively ox-LDL (25 hr), were recognized by the scavenger receptor on mouse peritoneal macrophages, (inhibition of [¹²⁵I]-ox-LDL macrophage degradation by acetyl LDL). By contrast, neither acetyl-LDL nor polyinosinic acid inhibited macrophage degradation of aggr. ox-LDL, suggesting internalization by an alternate process. Thus, ox. of LDL leads to different structural and functional characteristics, depending on the degree of ox.

Identification of a Lipid-Free Apo(a)-Apo B Complex in the d>1.2 Fraction of Plasma

Akira Yashiro, June O'Neill, and Henry F. Hoff

Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio

Although studies have reported the binding of apo(a)-apo B complexes eg. (a)-B to different lipoprotein species, identification of lipid-free (a)-B in plasma has not been reported. To identify such complexes, we subjected human plasma to density gradient ultracentrifugation and documented immunoreactive apo(a) and apo B in the d>1.2 fraction by appropriate RIAs. Moreover (a)-B was similar to delipidated Lp(a) in 1% agarose electrophoresis. On non-denaturing PAGE (2.5-7.5% gradient), an MW of 10'KD was found for the apo(a)-B complex. On SDS-PAGE, one major band was found under non-reducing conditions which immunostained for both apo(a) and apo B. Under reducing conditions, two major bands were seen, one staining for apo(a) and one for apo B. (a)-B from the d>1.2 plasma fraction bound and could be eluted from a Sepharose-anti-apo(a) column. This fraction containing only apo(a) and apo B, was lipid free, and mimicked delipidated Lp(a) by the above-described procedures. Thus, plasma contains a lipid-free apo(a)-apo B complex that could bind under specific metabolic conditions to different lipoprotein fractions.

Somatostatin and Its Analogue, Angiopeptin, Inhibit Adhesion of Leukocytes to Rat Heart Endothelial Cells

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Georgetown University Medical Center, Washington, D.C.

The effect of somatostatin (ST) and its analogue Angiopeptin (AP) on *in vitro* adhesion of rat spleen leukocytes (LC) to unstimulated and IL-1 β stimulated rat heart endothelial cells (EC) was studied. ST and AP inhibited LC adhesion to EC. The strongest inhibition was observed after 24 hours exposure.

Unstimulated EC bound 208 \pm 89 LC/mm². Treatment with ST or AP (0.6-10 μ M) for 24h decreased binding to 124 \pm 35 LC/mm² and 118 \pm 60 LC/mm², respectively ($p<0.001$). EC stimulated for 4h with IL-1 β (100U/ml) bound 1,045 \pm 52 LC/mm². ST (0.6 μ M) reduced binding to 292 \pm 31 LC/mm² ($p<0.01$). AP (1 μ M) was less potent and reduced binding to 811 \pm 75 LC/mm² ($p<0.05$). However, effect of AP was longer lasting (up to 24h). In conclusion, Angiopeptin may have a potential application in immune related cardiac vascular disease due to its prolonged inhibitory effect on IL-1 β induced LC-EC adhesion.

Plasma Lipoproteins Specifically Bind Thrombospondin (TSP)

Akihiko Muraishi, Maria A. Kowalska, Vicki R. Rothman, David M. Capuzzi, and George P. Tuszynski

Department of Medicine, Medical College of Pennsylvania, Philadelphia, Pa.

The present study explored the potential interaction between TSP and plasma lipoproteins using an *in vitro* binding assay. Human plasma lipoproteins VLDL, LDL, HDL, and apolipoproteins AI and AII were immobilized on microtiter plates and TSP binding was determined immunochemically with a polyclonal anti-TSP antibody. We found that human TSP bound saturably to all the plasma lipoproteins tested. Binding was maximal in the presence of 1 mM Ca²⁺/Mg²⁺ and was only partially inhibited with 2 mM EDTA. RGD peptides had no effect on binding. In contrast, TSP binding to fibrinogen was completely ion dependent. The concentrations of TSP that produced half maximal binding for VLDL, HDL, LDL, apo AI, and apo AII were 36.8, 12.4, 23.7, 6.9, and 18 nM, respectively. These data demonstrate that TSP can specifically interact with lipoproteins and suggest a potential role for TSP in the metabolism of lipoproteins, in their deposition into the vessel wall, and in atherogenesis.

The Association Between Carotid Arterial Wall Thickness and Active and Passive Cigarette Smoking

George Howard, Moyes Szklo, Gregory Evans, Grethe Tell, John Eckfeldt, Gerardo Heiss, and the ARIC Investigators

Bowman Gray School of Medicine, Winston Salem, N.C.

The effect of cigarette smoking on the carotid artery far wall thickness was considered in the white population from the Atherosclerosis Risk in Communities (ARIC) study. The population was divided into 2,460 current smokers, 3,448 past smokers, 2,440 who never smoked but reported weekly exposure to environmental cigarette smoke (ETS or "passive smoking"), and 1,306 who never smoked with no exposure to ETS. Age proved to affect the differences between smoking status classes ($p\leq 0.0001$), while gender had no effect ($p>0.05$). Within 5-year age groups there was a consistent gradient of wall thickness across the smoking exposure categories (mean \pm S.E. in millimeters):

Age group	No. exposure	ETS only	Past smoker	Current smoker
45-50	0.63 \pm 0.006	0.66 \pm 0.004	0.68 \pm 0.005	0.69 \pm 0.006
51-55	0.68 \pm 0.008	0.69 \pm 0.006	0.75 \pm 0.006	0.77 \pm 0.008
56-60	0.71 \pm 0.007	0.74 \pm 0.006	0.82 \pm 0.008	0.84 \pm 0.010
61-65	0.77 \pm 0.011	0.78 \pm 0.009	0.88 \pm 0.010	0.90 \pm 0.015

Using analysis of covariance, differences between no exposure and ETS were significant only at younger ages ($p<0.0001$), while differences between ETS and past smoking, or between past and current smoking, were significant only for older ages. This graded relationship underscores the importance of smoking as a risk factor for atherosclerosis.

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HOWARD, G., SZKLO, M., EVANS, G., TELL, G., ECKFELDT, J., HEISS, G. AND THE ARIC INVESTIGATORS, "THE ASSOCIATION BETWEEN CAROTID ARTERIAL WALL THICKNESS AND ACTIVE AND PASSIVE CIGARETTE SMOKING," ARTERIOSCLEROSIS AND THROMBOSIS 11(5): 1432A, 1991.

HOWARD, G., SZKLO, M., EVANS, G., TELL, G., ECKFELDT, J. AND HEISS, G., "PASSIVE SMOKING AND CAROTID ARTERY WALL THICKNESS: THE ARIC STUDY," CIRCULATION 85(2): 3, 1992.

An abstract, from the Bowman Gray School of Medicine (Winston Salem, North Carolina), based on a presentation at a November 1991 American Heart Association meeting, reported that ETS exposure was associated with thickness of the walls of the carotid arteries. (Howard, et al., 1991) The importance of carotid artery thickness is that it may be an indication of the severity of atherosclerotic involvement. Atherosclerosis of the carotid arteries is believed to underlie certain forms of stroke. These data were updated in a presentation at a March 1992 cardiovascular disease epidemiology conference, the abstract from which included information on some additional subjects, but otherwise reported similar results. (Howard, et al., 1992)

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Dietary Fat Intake and Carotid Artery Wall Thickness: The ARIC Study

Grethe S. Tell, Gregory W. Evans, Tomoko Shimakawa, Aaron R. Folsom, Myra Carpenter, Gerardo Heiss, for the ARIC Investigators. Bowman Gray School of Medicine, Winston-Salem, NC

We report preliminary results on the association between dietary fat intake and carotid artery wall thickness (WT) (measured by B-mode ultrasound) in 2114 black women (BW), 1316 black men (BM), 5193 white women (WW) and 4614 white men (WM) ages 45-64 years, examined by the Atherosclerosis Risk in Communities (ARIC) Study. A food frequency questionnaire was used to assess habitual dietary intake. Shown below are age- and energy-adjusted beta coefficients for the relation between WT (in mm) and average daily intake (see table for units):

	BW	BM	WW	WM
Animal fat (100 g/day)	.056*	.055	.101*	.070*
Vegetable fat (100 g/day)	-.074*	-.081	-.069*	-.080*
Monounsaturated fat (100 g/day)	.005	-.018	.082	.056
Saturated fat (100 g/day)	.085	.036	.133*	.031
Polyunsaturated fat (100 g/day)	-.110	-.248	-.163*	-.151
Cholesterol (100 mg/day)	.005*	.006	.010*	.005*

* $p < 0.05$ * $p < 0.01$ * $p < 0.001$ * $p < 0.0001$
Thus, elements of habitual dietary intake are consistently associated with WT in all four race-gender groups, consistent with their putatively atherogenic and anti-atherogenic properties.

Passive Smoking and Carotid Artery Wall Thickness: The ARIC Study

George Howard, Moyes Szklo, Gregory Evans, Grethe Tell, John Eckfeldt, Gerardo Heiss. Bowman Gray School of Medicine, Winston-Salem, NC.

The association between passive and active cigarette smoking with carotid artery wall thickness was studied in 12,863 men and women ages 45 to 64 examined by the Atherosclerosis Risk in Communities (ARIC) Study. Of these, 3,509 were current smokers, 4,276 past smokers, 3,316 had never smoked but reported exposure to environmental tobacco smoke (ETS or "passive smoke"), and 1,762 had never smoked and reported no exposure to ETS. Carotid artery wall thickness was measured by B-mode ultrasound. Increasing exposure to cigarette smoke across the gradient from never smoking to current smoking was consistently associated with increases in carotid artery wall thickness within 5-year age groups (shown below adjusted for race and gender, mean \pm S.E., in mm.):

Age Group	No Exposure	ETS Only	PAST Smoker	CURRENT Smoker
45-50	0.66 \pm 0.005	0.67 \pm 0.003	0.68 \pm 0.004	0.70 \pm 0.004
51-55	0.71 \pm 0.007	0.71 \pm 0.005	0.73 \pm 0.005	0.76 \pm 0.006
56-60	0.75 \pm 0.007	0.76 \pm 0.006	0.79 \pm 0.007	0.83 \pm 0.008
61-65	0.79 \pm 0.009	0.80 \pm 0.008	0.85 \pm 0.009	0.89 \pm 0.012

The ETS group had thicker arterial walls than never smokers; these differences were statistically significant ($p \leq 0.0001$) only at younger ages. Also, the ETS participants showed an increase ($p = 0.03$) in arterial wall thickness with an increasing number of hours per week of ETS exposure. Thus exposure to ETS may contribute to atherogenesis.

Comparison of Intracerebral Arterionecrosis in Japanese Men in Japan and Hawaii

Dwayne Reed, David Jacobs, Takuji Hayashi, Hiroyasu Iso, Masamitsu Konishi, James Nelson, Jack Strong. Honolulu Heart Program, Honolulu, HI

In earlier reports we showed that the incidence and mortality rates of all types of stroke were threefold greater in Japanese men in Japan compared to those in Hawaii, and that this difference was not related to atherosclerosis in the Circle of Willis. In this study, brain specimens from 232 men from a Hiroshima cohort, and 175 men in a Hawaii cohort were examined by three pathologists for the presence of different stages of arterionecrosis in small intracerebral arteries. Most measures of arterionecrosis were higher in all age groups in Japan than Hawaii; were higher among men who died of stroke compared to non-cardiovascular causes; and, were higher among men with cerebral infarction at autopsy. Risk factor analyses for the Hawaii cohort indicated that blood pressure and some aspect of the Asian diet were associated with arterionecrosis. These data indicate that the difference in stroke frequency between Japan and Hawaii is related to intracerebral arterionecrosis.

Depression Amplifies the Association Between Carotid Atherosclerosis and Age, Hypertension, Low Density Lipoproteins, and Platelet Aggregability

George A. Kaplan, Richard D. Cohen, Thomas W. Wilson, Jussi Kauhanen, Riitta Salonen, Jukka T. Salonen. California Department of Health Services, Berkeley, CA

Extensive data on cardiovascular risk factors, ultrasound readings of the intimal-media thickness (IMT) of the common carotid artery, and MMPI depressive status were obtained from 825 participants in the Kuopio Ischemic Heart Disease Risk Factor Study, a population-based study of 42-60 year old men in Eastern Finland. In multiple regression models predicting IMT, there were significant interactions between MMPI depression (above vs. below median) and age ($p = .049$) and LDL ($p = .028$). An 18 year difference in age was associated with 40% greater increase in IMT in the depressed than in the non-depressed. A median split in LDL levels was associated with a 2-fold increase in IMT among the depressed.

Three way interactions in predicting IMT were found for age*depression*platelet aggregability ($p = .072$), and age*depression*hypertension ($p = .078$). Depression was associated with 79% greater age-related increase in IMT for those with high platelet aggregability and a 9% greater increase in hypertensives. There were no significant interactions between depressive status and fibrinogen, smoking, alcohol consumption, or physical activity and IMT. The results indicate that a psychosocial factor, depression, may contribute to the development of atherosclerotic vascular disease by increasing the impact of other risk factors on atherogenesis.

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ZHU, B.-Q., SUN, Y.-P., SIEVERS, R.E., ISENBERG, W.M., GLANTZ, S.A. AND PARMLEY, W.W., "PASSIVE SMOKING INCREASES EXPERIMENTAL ATHEROSCLEROSIS IN CHOLESTEROL-FED RABBITS." JACC 21(1): 225-32, JANUARY 1993.

This was a laboratory study in which rabbits on a high cholesterol diet were exposed, eight rabbits at a time, to either a high or a low dose of "ETS" over a 10-week period. The "high ETS" group was exposed to sidestream smoke (four cigarettes every 15 minutes, 6 hours/day, 5 days/week). The "low ETS" group was exposed to diluted mainstream smoke. After 10 weeks on this regimen, aortic and pulmonary arterial samples were examined for indications of lipid lesions, which were taken as a measure of atherosclerotic development. The authors concluded that ETS exposure was associated with evidence of atherosclerosis.

Our present study shows that passive smoking significantly increases aortic and pulmonary artery atherosclerosis in cholesterol-fed rabbits in a dose-dependent manner. (p. 230, col. 1)

Zhu et al. also reported that bleeding times were shorter in the ETS exposed groups, suggesting an adverse effect on platelet function.

This study suffers from several major flaws, some of which are indicated below.

1. None of the rabbits were exposed to ETS. One group was exposed to sidestream smoke and the

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other to mainstream smoke. Thus, the potential relevance of these data to ETS exposure is unknown.

2. Rabbits were fed a high-cholesterol diet. The role of this dietary factor on the results reported is unknown.
3. The arterial analyses were based on measurements of "lipid lesions," whose relationship to the development of atherosclerosis in humans is uncertain.
4. Exposing the rabbits to heavy concentrations of sidestream or mainstream smoke, especially when such exposure occurred in a crowded cage, may have introduced a variety of confounding factors, particularly a stress factor.
5. Whole-body tobacco smoke exposure, with several animals in the same cage at the same time, makes exposure conditions poorly defined. In particular, there is the likelihood that there may have been oral intake of deposited particulate matter on the animals' fur which

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they may have ingested during preening. Or, perhaps, animals might bury their noses in each other's fur which would alter the nature and amount of smoke exposure.

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EXPERIMENTAL STUDIES

Passive Smoking Increases Experimental Atherosclerosis in Cholesterol-Fed Rabbits

BO-QING ZHU, MD, YI-PING SUN, MD, RICHARD E. SIEVERS, BS, WILLIAM M. ISENBERG, PhD, STANTON A. GLANTZ, PhD, FACC, WILLIAM W. PARMLEY, MD, FACC

San Francisco, California

Objectives. We evaluated the influence of passive smoking on experimental atherosclerosis in cholesterol-fed rabbits.

Background. Exposure to environmental tobacco smoke (ETS) has been epidemiologically linked to death from ischemic heart disease in nonsmokers.

Methods. New Zealand male rabbits were randomly divided into three groups after 2 weeks of a 0.3% cholesterol diet. Sixteen rabbits were exposed to a high and 16 rabbits to a low dose of ETS; 32 rabbits located in another room served as an unexposed control group. After 10 weeks of ETS exposure, all rabbits were killed, and the percent of aortic and pulmonary artery endothelial surfaces covered by lipid lesions was measured by staining and planimetry.

Results. Average air nicotine, carbon monoxide and total particulate concentrations were 1,040 $\mu\text{g}/\text{m}^3$, 60.2 ppm and 32.8 mg/m^3 for the high dose ETS group, 30 $\mu\text{g}/\text{m}^3$, 18.8 ppm and 4.0 mg/m^3 for the low dose ETS group and <1 $\mu\text{g}/\text{m}^3$, 3.1 ppm and 0.13 mg/m^3 for the control group. The percent atherosclerotic

involvement of the aorta and pulmonary artery increased significantly with ETS exposure (for the aorta, $30 \pm 19\%$ [mean \pm SD] for the control group, $36 \pm 14\%$ for the low dose ETS group and $52 \pm 21\%$ for the high dose ETS group, $p < 0.001$; for the pulmonary artery, $22 \pm 15\%$ for the control group, $29 \pm 25\%$ for the low dose ETS group, and $45 \pm 12\%$ for the high dose ETS group, $p < 0.001$). Bleeding time was significantly shorter in the two ETS groups than in the control group (86 ± 17 vs. 68 ± 15 , 68 ± 18 s, $p < 0.001$). There were no significant differences in serum triglycerides, cholesterol and high density lipoprotein cholesterol at the end of the study.

Conclusions. Environmental tobacco smoke affects platelet function and increases aortic and pulmonary artery atherosclerosis. This increase of atherosclerosis was independent of changes in serum lipids and exhibited a dose-response relation. These results are consistent with data from epidemiologic studies demonstrating that ETS increases the risk of death due to heart disease.

(*J Am Coll Cardiol* 1993;21:225-32)

Environmental tobacco smoke (ETS) is the term used to describe tobacco combustion products inhaled by nonsmokers in the proximity of burning tobacco. More than 4,000 constituents have been identified in cigarette smoke. Most exposure to ETS is from sidestream smoke emitted from the burning tip of the cigarette. Sidestream smoke is hazardous because it contains high concentrations of ammonia, benzene, nicotine, carbon monoxide and many other carcinogens and irritants (1-3).

Passive smoking involves breathing both sidestream smoke that goes directly into the air from the burning tobacco products and mainstream smoke after it has been exhaled by smokers. Sidestream smoke has higher concentrations of nox-

ious compounds than does mainstream smoke. It has been estimated that approximately 50 million nonsmoking adults over the age of 35 years are regularly exposed to environmental tobacco smoke. Additionally, 50% of all children live in families with one or more smokers (4). The effects of passive smoking on health have been reported to include short-term effects, such as exacerbation of asthma and angina, as well as long-term effects, such as increased risk of lung cancer, respiratory tract infection and atherosclerosis (1-7).

Environmental tobacco smoke adversely affects platelet function and damages arterial endothelium, and depresses cellular respiration at the level of mitochondria (4,5). People exposed to it have significantly thicker arterial walls than do unexposed nonsmokers, and wall thickness is increased with increasing exposure (8). Passive smokers also have significantly depressed high density lipoprotein (HDL) cholesterol levels and significantly elevated ratios of total cholesterol to HDL cholesterol levels (9).

The materials in ETS may thus accelerate the development of atherosclerotic plaque. Previous experimental studies, however, showed that exposure to smoke from only 1 cigarette/day for 11 to 13 months failed to quantitatively affect atherosclerosis or serum lipids (10). We designed the present study to further evaluate the influence

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of passive smoking on atherosclerosis in cholesterol-fed rabbits.

Methods

Protocol. Sixty-four New Zealand male rabbits (2.0 to 2.6 kg) were randomly separated into three groups and fed a high cholesterol diet for 12 weeks. The cholesterol diet (Ziegler Bros., Inc.) contained 3% soybean oil and 0.3% cholesterol by weight. The rabbits were housed in separate cages in well mixed exposure chambers (BioClean, Duo, Flo, model H 5500, Lab Products Inc.), 1.92 m × 1.92 m × 0.97 m (3.58 m³), that accommodated eight rabbits in each group.

After 2 weeks on the diet, 16 rabbits, 8 at a time, were exposed to a high dose of sidestream smoke (high ETS group) from Marlboro filter cigarettes (4 cigarettes every 15 min for 6 h/day, 5 days/week) using a smoking machine (Heinr. Borgwaldt GMBH RM 1/G, D-2000 Hamburg, Germany) for 10 weeks from week 2 to week 12. Another 16 rabbits, 8 at a time, were given a low dose of smoke (low ETS group) from the same smoking machine through 20.5 feet of 10-mm inside diameter plastic tube attached to the mainstream port on the smoking machine. The smoke cooled and the large particles settled out in this tube, making the exposure level of the low ETS group similar to that of smoke spread by the ventilation system of a building from an area where smoke was permitted to nonsmoking areas of the same building. Thirty-two rabbits, 16 at a time, located in the same type of exposure chamber in another room but with no smoking machine, served as a control group eating the same diet for 12 weeks. Three fans in the exposure chambers were adjusted to ensure good mixing, using the measurement devices discussed later. At the end of the 6-h exposure period, the exhaust fan on the Bioclean unit was turned on and rapidly lowered the level of ETS pollution in the exposure chamber to background levels corresponding to those of the control animals until next day when the Bioclean unit was turned off and the smoking machine was turned on again.

Monitoring smoke exposure inside the chambers. We measured several constituents of ETS in the three exposure chambers: carbon monoxide (CO), total particulates, respirable suspended particulates and nicotine.

To measure average carbon monoxide concentrations during the 6-h exposure period, we used a model L15 CO Personal Exposure System (Langan Products) every other week for the three groups. We obtained an average daily value taken from 2,520 samples during the exposure period (3 h of ETS, 1 h break, 3 h of ETS) (Fig. 1).

To measure total particulate concentrations, we used a Miniram PDM-3 Optical Scattering Particle Monitor (MIE, Inc.), monitoring particulate concentration every 10 s, and computed average total particulate concentrations during the exposure period (Fig. 2). We obtained these data every other week for all three groups. We also used a Piezobalance

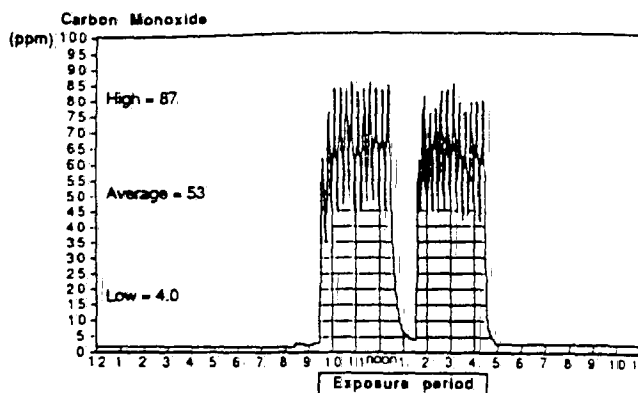


Figure 1. Representative carbon monoxide (CO) concentrations during a 24-h period. During the period of exposure to environmental tobacco smoke (ETS) (3 h of ETS, a 1-h break, 3 h of ETS), the average CO value from 2,520 samples is 53 ppm.

Respirable Aerosol Mass Monitor (model 3500 Thermo-System) to measure respirable suspended particulates (11) on 4 different days, about 10 samples/day; to calibrate the Miniram. The Piezobalance was factory calibrated before the study.

The Piezobalance measures the smaller respirable, suspended particulates, whereas the Miniram measures total particulates. To determine the relation between particulate concentrations measured by the Miniram and Piezobalance, we measured average particulate concentration values (37 values, each an average of 3 measurements) at different levels of ETS using these two instruments simultaneously. Figure 3 shows that there was a strong linear relation between average particulate concentrations measured by the Piezobalance and the Miniram, with the Piezobalance reading about 36% of that obtained by the Miniram. This relation is similar to that found in a previous study (12) in which the Miniram and the Piezobalance were compared in an environmental chamber measuring ETS over a range of concentrations.

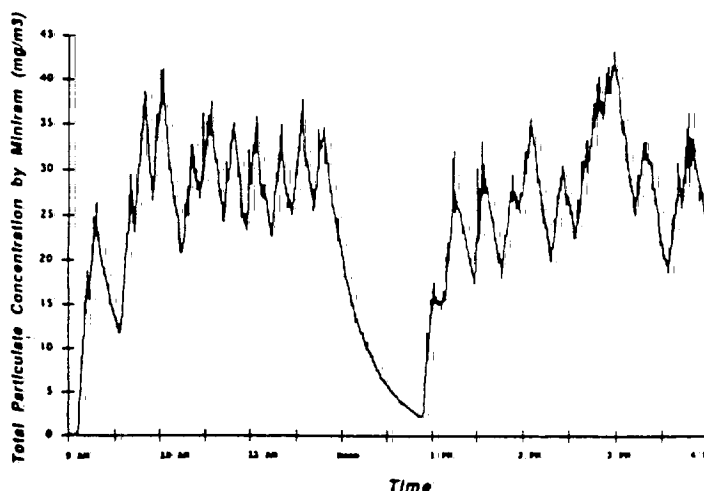
In addition, we monitored air nicotine levels by using a passive diffusion monitor (13) that was located in the middle of the exposure chamber during the 6-h exposure period, every other week for all three groups.

Hematologic and biochemical analysis. Bleeding time, circulating platelet aggregates, platelet count, hematocrit, hemoglobin, total serum cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol and serum cotinine were measured at the beginning of the study (before the rabbits started the high cholesterol diet) and at 6-week intervals (that is, after 4 and 10 weeks). The concentration of cotinine was determined by gas chromatography with nitrogen-phosphorus detection (14). This method has been modified for simultaneous extraction of cotinine and determination using capillary gas chromatography (15).

Bleeding time was determined after 1-min warming of the rabbit's ear in a normal saline bath (37°C). A small standard

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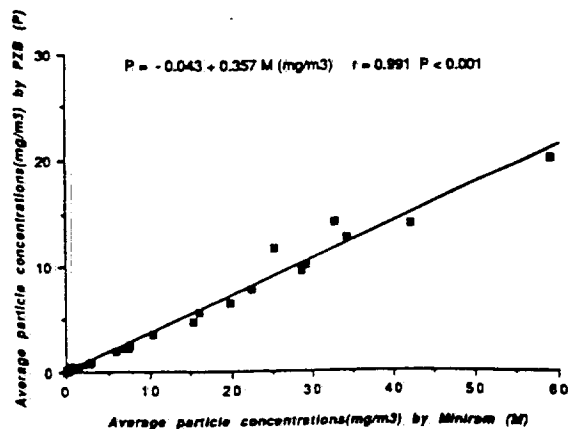
Figure 2. Total suspended particulate concentrations measured by the Miniram every 10 s during a representative period of exposure to environmental tobacco smoke (ETS) (3 h of ETS, a 1-h break, 3 h of ETS). Average total suspended particulate concentration during the exposure period was 23.7 mg/m^3 . The peaks occur while the cigarettes are actually being smoked. The large drop corresponds to the 1-h midday break.



prick was made in the ear, avoiding macroscopic vessels. The time from the initial bleeding to cessation of bleeding was recorded as the bleeding time.

A platelet count ratio method (16) was used for quantitative determination of circulating platelet aggregates. One mmol/liter adenosine diphosphate was added to a citrated venous blood sample before stirring. The sample was divided into two tubes, one containing ethylenediaminetetraacetic acid (EDTA)/formalin solution and the other EDTA only. Platelet-rich plasma was collected after centrifugation. Platelets in both samples were counted, using standard techniques (Sequoia-Turner Corporation, Operator Reference manual, Cell-Dyn 900 Hematology Analyzer). The platelet aggregate ratio was calculated from the platelet count in the two solutions. The higher the ratio, the fewer the platelet aggregates.

Figure 3. Relation between average particulate concentrations measured by the Piezobalance (PZB) and the Miniram. Because of the excellent linear relation, one can measure respirable suspended particulates by taking 36% of the readings obtained with the Miniram.



Total serum cholesterol and triglyceride levels were determined by automated enzymatic methods (Coulter DART cholesterol reagent using the DACOS and DACOS XL analyzers), and HDL cholesterol concentrations were measured after precipitation of other lipoprotein classes with dextran and magnesium ions (HDL cholesterol precipitant (Cat No 236141), Ciba Corning Diagnostics Corp.).

The blood samples were drawn in the morning (Tuesday to Friday) after 12 h of fasting and before ETS exposure. The samples for plasma cotinine analysis also were taken in the morning before exposure (17 h after the last ETS exposure).

Morphologic studies. At week 12, after 10 weeks of exposure to ETS (or control conditions), all rabbits were killed. After intravenous administration of pentobarbital, 130 mg/kg body weight, the aorta was removed from its origin (2 cm distal to the aortic valve) down to the bifurcation of the internal iliac arteries; the pulmonary artery was isolated from its beginning at the pulmonary valve to just above the bifurcation. The vessels were opened by linear vertical incision, fixed in a 10% formalin solution for 24 h, stained with Sudan IV, then photographed. Finally, planimetric measurement of lipid lesions was performed quantitatively by estimating the total stained regions in photographs of each artery with a planimeter. The measurements were performed in blinded fashion and in duplicate.

Statistical analysis. The text and tables list data as the mean value \pm SD; the figures summarize data as the mean value \pm SEM. Data were analyzed by linear regression, using ETS dose as the independent variable. Multiple linear regression was also used with aortic and pulmonary artery lesions as the dependent variables, including cholesterol levels as well as exposure to smoke in the regression equation to account for the possible effects of different serum cholesterol levels on the extent of lesions. Analysis of variance (ANOVA) was used to compare observations among the three experimental groups. Data were analyzed before and after exposure, as well as in terms of changes in

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Table 1. Average Air Nicotine, Carbon Monoxide and Particulate Concentrations in the Control and Environmental Tobacco Smoke Chambers

Group	Air Nicotine ($\mu\text{g}/\text{m}^3$)	Air CO (ppm)	Total Particulates* (mg/m^3)	Respirable Particulates† (mg/m^3)
Control	<1 (n = 1)	3.1 \pm 1.9 (n = 2)	0.13 \pm 0.04 (n = 10)	0.07 \pm 0.06 (n = 10)
Low ETS	30 \pm 3 (n = 4)	18.8 \pm 2.2 (n = 5)	4.03 \pm 0.49 (n = 3)	1.2 \pm 0.7 (n = 8)
High ETS	1,040 \pm 302 (n = 4)	60.2 \pm 14.3 (n = 5)	32.8 \pm 6.9 (n = 7)	13.8 \pm 3.5 (n = 6)

*By Minum; †By Piezobalance. Values are expressed as mean value \pm SD. n = the number of samples. For nicotine, carbon monoxide (CO) and total particulates, each of the n samples represents the average value observed during the exposure period (3 h of environmental tobacco smoke [ETS], 1 h break, 3 h of ETS) on 1 day. For example, the n = 2 values for Air CO in the control group represent average values recorded during 7 h on 2 different days. For respirable particulates, the sample size represents the actual number of simple samples taken while the smoke levels were at steady state.

the measured variables before and after the 10-week exposure period using paired *t* tests. We did not combine all data into a single two-factor analysis of variance (with time [before or after exposure] as one factor and ETS group [control, low ETS, high ETS] as the second factor); we believed that with such an approach the presence of a control group (with no exposure) at both times would generally lead to a significant interaction between time and exposure group that would make the results of tests on the main effects difficult to interpret. Data were processed by using Minitab Versions 7.2 and 8.2. A *p* value < 0.05 was taken as statistically significant.

Results

Weight gain. There was a similar initial body weight and subsequent weight gain in all three groups of rabbits throughout the 12-week period. The average body weight before (week 2) and after 10 weeks of ETS exposure (week 12) was 2.7 \pm 0.3 and 3.6 \pm 0.3 kg, respectively. There was no significant difference in weight of the rabbits as assessed by ANOVA before (*p* = 0.344) or after (*p* = 0.306) the 12-week experimental period. Similarly, ANOVA showed no significant differences in weight gain among the three exposure groups (0.87 \pm 0.29 kg for the control group, 0.88 \pm 0.37 kg for the low ETS group and 0.91 \pm 0.36 kg for the high ETS group, *p* = 0.923) or in food intake among the three groups, either before (*p* = 0.398) or after (*p* = 0.431) exposure to ETS. The average food intake before and after ETS exposure was 178 \pm 46 and 164 \pm 58 g/day, respectively. The similarities in eating and weight gain across time and the

different exposure groups indicate that any differences observed in the exposure groups were not due to dietary differences. There were no deaths during the 12-week study.

Smoke exposure inside the chamber. The average air nicotine, carbon monoxide (CO) and total particulate concentrations during the 6-h exposure period are listed in Table 1. There were large differences in air nicotine, CO and particle concentrations between the groups with a high or low level of ETS exposure and the control group and between the high and low ETS groups during the period of exposure.

Alterations in lipids. After rabbits were fed a high lipid diet, the serum cholesterol increased considerably in all animals during the 12-week period. The serum lipid levels for the three groups (Table 2) show a similar increase in total serum cholesterol. Total cholesterol may have been slightly (*p* = 0.051) higher in the control group than in the two ETS groups before the 10-week exposure period. There was no significant difference (*p* > 0.8) among the three groups at the end of the experiment. There were no significant differences (*p* > 0.3) in triglycerides and HDL cholesterol among the two ETS groups and the control group either before or after the 10-week exposure period. There also were no significant differences (*p* > 0.4) in the area under the cholesterol time curve (cholesterol-weeks: 11,632 \pm 3,479 vs. 9,831 \pm 3,048 and 10,349 \pm 3,182 mg/dl-wk), change (12-week value minus 2-week value) in cholesterol (538 \pm 463 vs. 674 \pm 419 and 729 \pm 627, 674 \pm 419 mg/dl), change in triglycerides (13 \pm 84 vs. -63 \pm 372 and 22 \pm 91 mg/dl) and change in HDL cholesterol (15 \pm 29 vs. 7 \pm 22 and 16 \pm 25 mg/dl),

Table 2. Effects of Environmental Tobacco Smoke on Serum Lipids in Cholesterol-Fed Rabbits

Group	Cholesterol (mg/dl)		Triglycerides (mg/dl)		HDL Cholesterol (mg/dl)	
	Before	After	Before	After	Before	After
Control (n = 32)	671 \pm 278	1,209 \pm 483	91 \pm 72	78 \pm 51	40 \pm 16	55 \pm 27
Low ETS (n = 16)	480 \pm 279	1,154 \pm 395	102 \pm 93	165 \pm 349	36 \pm 13	43 \pm 25
High ETS (n = 16)	531 \pm 246	1,260 \pm 532	119 \pm 93	98 \pm 111	37 \pm 15	50 \pm 21

Values are expressed as mean value \pm SD. There were no significant differences (*p* > 0.3) among the three groups except for total cholesterol before exposure to environmental tobacco smoke (ETS). Values in the control group were higher than values in the other two groups (*p* = 0.05). After = 12 weeks on lipid diet and 10 weeks of smoke exposure; Before = 2 weeks on lipid diet and before smoke exposure; HDL = high density lipoprotein.

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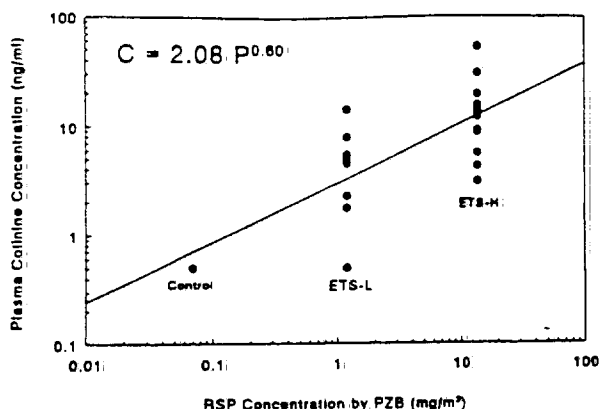


Figure 4. Relation between log-plasma cotinine levels and log-respirable suspended particulates (RSP) concentrations measured by Piezobalance (PZB). ETS-H and ETS-L = groups with a high or low level, respectively, of exposure to environmental tobacco smoke.

respectively, among the control group and the low and high ETS groups.

Cotinine levels in plasma. The plasma cotinine levels at the 6th week of ETS exposure in the control and the low and high ETS groups were <1.0 , 6.0 ± 4.3 and 15.6 ± 12.3 ng/ml, respectively. These cotinine levels are based on blood samples drawn in the morning before that day's exposure to ETS. Given the 20-h half-life of cotinine in the blood, the steady state cotinine levels at the end of the daily exposure period would be approximately <1 , 12 and 31.2 ng/ml, respectively, for the control and low and high ETS groups. There was a linear relation between log cotinine levels in plasma and log average respirable suspended particulate concentrations measured by Piezobalance ($r = 0.84$, $p < 0.001$) (Fig. 4).

Morphologic studies. Figure 5 shows the percentage of total aortic and pulmonary artery surface area covered by

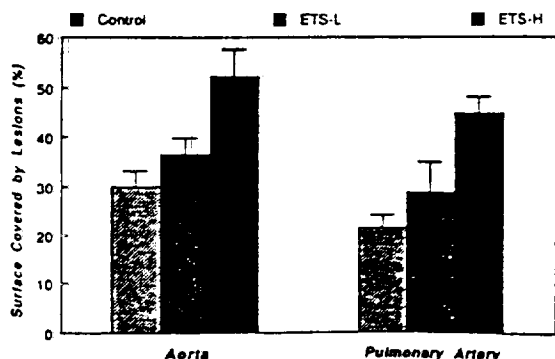


Figure 5. Percent of aortic and pulmonary artery surface areas covered by atherosclerotic lesions for each group. There is a significant ($p < 0.001$) dose-response relation for both vessels. Error bars are SEM. Abbreviations as in Figure 4.

lipid lesions in the three experimental groups. There was a significant ($p < 0.001$) dose-response relation for the extent of lipid lesions for both the aorta and the pulmonary artery as a function of respirable suspended particulate concentration measured by Piezobalance. Although the intercepts of the dose-response relations for the two arteries are significantly different ($31.3 \pm 2.7\%$ for the aorta vs. $23.0 \pm 2.6\%$ for the pulmonary artery, $p < 0.05$), the slopes are not ($1.62 \pm 0.41\%/mg/m^3$ vs. $1.69 \pm 0.39\%/mg/m^3$, $p > 0.5$). These results indicate that, although the baseline levels of lipid deposits in these two arteries are different, the effects of exposure to ETS on the two arteries are similar in terms of increased lipid deposits. There were also positive correlations ($r = 0.5$, $p < 0.001$) between the percent of lipid lesions in both arteries and the average CO levels. As with the relation between lesions and particulate concentration, the aorta initially had more lipid deposits than did the pulmonary artery, but both vessels showed similar increases ($\sim 0.5\%/ppm$) in lipid deposits with ETS exposure as CO was increased. Because particulate and CO levels are highly correlated, we cannot say whether either or both (or other) elements of the ETS are responsible for the dose-dependent increase in lipid deposits we observed. We can conclude unequivocally that there were significant ($p < 0.001$) dose-dependent increases in lipid deposits on both vessels with increasing ETS exposure.

Platelet function. Data on bleeding time, platelet aggregate ratio and platelet count are shown in Table 3. Bleeding times at week 12 in the low and high ETS groups were significantly shorter than those in the control group (68 ± 15 , 68 ± 18 vs. 86 ± 17 s, respectively, $p < 0.001$). This result demonstrates that there were large (20%) changes in bleeding time at low levels of exposure to ETS and that further increases in exposure did not produce an additional effect. The platelet aggregate ratio at week 12 in the high ETS group may have been lower than the control level (79.4 ± 10.7 vs. $88.0 \pm 12.2\%$, $p = 0.07$ by paired t test), reflecting an increase in platelet aggregates in the high ETS group. The platelet counts were modestly decreased to a similar extent in all three groups (Table 3). The changes in platelet count before and after exposure were -36 ± 97 , -84 ± 131 and -94 ± 95 ($p = 0.151$ by ANOVA), respectively. These data show effects on platelet function at low levels of ETS that do not increase with further increases in dose. This result suggests that platelets are sensitive to low levels of ETS, after which the effect is saturated.

Discussion

Active smoking has consistently been identified as a major risk factor for ischemic heart disease. Exposure to environmental tobacco smoke (ETS), as passive smoking, has now been linked to heart disease in nonsmokers (4,6,17-19). Epidemiologic studies conducted in a variety of locations reflect about a 30% increase in risk of death from ischemic heart disease or myocardial infarction among non-

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Table 3. Effects of Environmental Tobacco Smoke on Platelet Function in Cholesterol-Fed Rabbits

Group	Bleeding Time (s)		Platelet Aggregation (%)		Platelet Count (10^3)	
	Before	After	Before	After	Before	After
Control (n = 32)	78 \pm 23	86 \pm 17	84.1 \pm 14.6	80.9 \pm 13.7	295 \pm 89	256 \pm 89
Low ETS (n = 16)	73 \pm 26	68 \pm 15	83.9 \pm 11.8	82.6 \pm 14.3	352 \pm 130	268 \pm 95
High ETS (n = 16)	77 \pm 19	68 \pm 18	87.9 \pm 12.3	79.4 \pm 10.7*	372 \pm 140	293 \pm 76

*p < 0.01 compared with values in the control group. †p = 0.07, compared with values in the high ETS group before exposure. Values are expressed as mean value \pm SD. Abbreviations as in Table 2.

smokers living with smokers (4-6,18). The larger studies also demonstrate a significant dose-response effect, with greater exposure to ETS associated with a greater risk of death from heart disease.

Our present study shows that passive smoking significantly increases aortic and pulmonary artery atherosclerosis in cholesterol-fed rabbits in a dose-dependent manner. There was a strong positive correlation between the percent of atherosclerotic lesions and the average CO or particulate concentrations, with the lipid deposits in arteries in the high dose group nearly doubling in just 10 weeks. These results are consistent with epidemiologic studies demonstrating that ETS increases the risk of death from heart disease.

Passive smoking and atherosclerosis. Smoking has long been recognized as one of the major risk factors for adult coronary heart disease, peripheral arterial disease, abdominal aortic aneurysm and stroke. Clinical investigations indicated that the proportion of intimal surface involved with atherosclerotic lesions in both the aorta and the right coronary artery was positively associated with serum very low density lipoprotein and low density lipoprotein cholesterol and was negatively associated with serum HDL cholesterol. The serum thiocyanate concentration, a marker for smoking, was strongly associated with the prevalence of atherosclerotic lesions, particularly in the abdominal aorta (20). Population studies of passive smokers revealed that passive smokers had significantly thicker carotid arterial walls than those of persons who had never smoked passively or actively (8). Our results are consistent with what one would expect from these clinical studies.

However, we observed much larger effects of ETS than would be expected from a simple dose-based extrapolation from high doses experienced by smokers to the lower doses of smoke experienced by nonsmokers. Our results suggest that nonsmokers may be more sensitive to the toxins in ETS than smokers are, perhaps because smokers have somehow adapted to the chronic poisoning associated with active smoking. It is also probable that some of the biochemical systems involved are very sensitive to ETS but saturate at low doses.

Passive smoking and serum lipids. Epidemiologic studies have suggested that there is a dose-response relation between the number of cigarettes smoked/day and increasing levels of plasma cholesterol (21). The HDL cholesterol level was lower in children exposed to ETS; the HDL₂ subfraction

was reduced in boys, whereas the HDL₃ subfraction was reduced in girls. As a result, exposure of children to ETS may increase the risk of premature coronary heart disease (22). Nonsmoking adolescents with two smoking parents had significantly higher plasma cotinine concentrations after an adjustment for other factors than did adolescents whose parents did not smoke. A plasma cotinine concentration >2.5 μ g/ml was associated with an 8.9% greater ratio of total cholesterol to HDL cholesterol and a 6.8% lower HDL cholesterol level (23). Similar results have been reported for nonsmoking adults exposed to ETS in the workplace (9). These results suggest that passive smoking, like active smoking, leads to alterations in lipid profiles predictive of an increased risk of atherosclerosis.

The present study, however, showed no significant differences in total serum cholesterol, triglycerides, HDL cholesterol, cholesterol-weights, change in cholesterol, change in triglycerides or change in HDL cholesterol between the control group and the two passive smoking groups.

To test whether the changes in lipid lesions associated with ETS exposure could be a result of differences in cholesterol levels, we performed a multiple regression analysis with the percent aorta and pulmonary artery with lipid deposits as the dependent variables and cholesterol, triglycerides and HDL cholesterol levels at 2 and 12 weeks (that is, before and after ETS exposure control) and ETS concentration as the independent variables. In both cases ETS exposure was still significant (p < 0.001) and positively associated with ETS dose after accounting for differences in serum cholesterol. Therefore, the increase in atherosclerotic lesions in the cholesterol-fed rabbits exposed to ETS was independent of changes in serum lipids in the present study.

Passive smoking and platelet function. In addition to their role in acute thrombus formation, platelets have also been implicated in the development of atherosclerosis. Davis et al. (17) reported that mean values of the platelet aggregate ratio before and after passive smoking were 0.87 and 0.78, respectively (p = 0.002). These values are similar to those we observed in the high ETS group (Table 3). They found that passive smoking increased platelet aggregation with a magnitude similar to that observed in active smoking. The effects of cigarette smoking on the levels of platelet-activating factor (PAF), one of the most potent proinflammatory agents, or PAF-like lipids were studied (24,25). The

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results showed that the values of PAF-like lipids in both LDL and HDL in smokers increased significantly after smoking, and that the activity of plasma enzyme, PAF acetylhydrolase, was inhibited by cigarette smoke extract in a dose-dependent manner. The charge alteration reactions and PAF-acetylhydrolase inhibition appear to be localized at different sites on the lipoprotein molecule. Thus, the observed inhibition may account for the increase in plasma PAF concentration that is known to occur in smokers.

In the present study, bleeding times at week 12 in the two ETS groups were significantly shorter than in the control group ($p < 0.001$), and platelet aggregate ratio at week 12 in the high ETS group was borderline lower than the control level ($p = 0.07$), suggesting increased platelet aggregate formation. These results suggest that the effects of passive smoking may be mediated, at least in part, by altered platelet function.

Passive smoking and arterial endothelium. People exposed to ETS had a significantly thicker carotid artery wall than that of nonexposed persons who had never smoked, with the increase in wall thickness increasing with greater ETS exposure (8). Such epidemiologic studies are complemented by a variety of physiologic and biochemical data showing that ETS damages arterial endothelium. Davis et al. (17) reported that mean values of anuclear endothelial cell carcasses in venous blood before and after passive smoking were 2.8 and 3.7 ($p = 0.002$). The appearance of these cell carcasses indicates damage to the endothelium, which is the initiating step in the atherosclerotic process. Bondjers et al. (26) hypothesized that the effect of smoking might be mediated by increased catecholamine levels. The endothelial injury induced by smoking could be inhibited by metoprolol, supporting this hypothesis.

Other possible mechanisms of atherogenesis induced by ETS. Clinical studies (27-29) in smokers with coronary artery disease show that smoking increases myocardial oxygen demands and such indicators as the rate-pressure product). Also, smoking-induced coronary vasoconstriction, which is due to an alpha-adrenergically mediated increase in coronary artery tone, is prevented by calcium antagonist drugs and nitroglycerin. Thus, smoking can adversely affect the balance between myocardial oxygen supply and demand.

Several animal studies (5) have also shown that injections of polycyclic aromatic hydrocarbons, in particular 7,12-dimethylbenz(a,h) anthracene and benzo(a)pyrene, significantly increase aortic plaque and accelerate the development of atherosclerosis. These studies provide evidence that known carcinogenic chemicals can be atherogenic as well. In animal experiments, ETS also depresses cellular respiration at the level of mitochondria (30). The effects of ETS on cardiovascular function, platelet function, neutrophil function and plaque formation are the probable mechanisms leading to heart disease (4,5).

Dose and duration. In the present study, the average concentrations of air nicotine, CO and particles during 7 h of exposure in the high ETS group were 30-fold, 3-fold and

10-fold higher than in the low ETS group (1,040 vs. 30 $\mu\text{g}/\text{m}^3$, 60 vs. 19 ppm, 13.8 vs. 1.2 mg/m^3 , respectively). Human exposure studies (5,11,13) showed that nicotine and respirable suspended particulate levels in restaurants ranged from 1 to 25 $\mu\text{g}/\text{m}^3$ and 55 to 600 $\mu\text{g}/\text{m}^3$, respectively; respirable suspended particulate levels were 589 to 1,140 $\mu\text{g}/\text{m}^3$ in bars and bingo halls (3). The U.S. National Ambient Air Quality Standard for respirable particles is 50 $\mu\text{g}/\text{m}^3$ (annual average). The nicotine levels in smoking sections on airplanes were found to be 50 to 100 $\mu\text{g}/\text{m}^3$. Air nicotine, CO and respirable suspended particulate levels in some public smoking rooms were found to range from 50 to 500 $\mu\text{g}/\text{m}^3$, 5 to 50 ppm and 0.50-1.95 mg/m^3 , respectively. Thus, the levels we observed in the high ETS group are a factor of 2 to 10 higher than those observed in routine human environments and the levels in the low ETS group are similar to those of heavily smoking-polluted, but realistic, human environments.

The studies (31) reviewed show that cotinine measurements are sensitive to the current exposure of nonsmokers to other people's tobacco smoke with a half-life of ≈ 20 h in the blood. Plasma cotinine levels after 2 h of exposure to ETS in a heavily polluted public house were 7.33 ng/ml. The cotinine levels in plasma we observed in the low ETS group were comparable to those of a heavily polluted room, whereas those in the high ETS group were two- to fourfold higher.

Despite exposure to higher than routine human exposure levels, every rabbit in the two ETS groups tolerated the exposure well during the 10-week exposure period. There were no differences in food consumption or weight gain among the different experimental groups. The differences between these experimental exposure levels and actual human exposure levels were small compared with those of other studies of environmental toxins, where extrapolations >5 to 6 orders of magnitude are common. Indeed, our low ETS group represented realistic exposure for people who work in smoking environments, such as bartenders or waiters working in the smoking section of a restaurant.

Conclusions. These data indicate that the exposure of lipid-fed rabbits to passive smoke adversely affects platelet function and significantly increases atherosclerotic lesions in the aorta and pulmonary artery. This increase in atherosclerosis is independent of changes in serum lipids and has a dose-response relation. These results are consistent with epidemiologic studies demonstrating that ETS increases the risk of death from heart disease.

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2023512297

TRIBBLE, D.L. AND FORTMANN, S.P., "REDUCED PLASMA ASCORBIC ACID CONCENTRATIONS IN WOMEN REGULARLY EXPOSED TO ENVIRONMENTAL TOBACCO SMOKE (ETS), CIRCULATION 86(4): I-675, 1992.

There have been limited data in the literature suggesting that certain vitamins might be a factor in the development of heart disease. Based on this theory, a 1992 meeting abstract measured dietary and plasma levels of vitamin C (ascorbic acid) in people exposed to ETS. Compared to a control group, ETS-exposed nonsmokers were reported to have decreased plasma levels and dietary intake of ascorbic acid. The authors concluded:

These results suggest that suboptimal AA [ascorbic acid] nutriture may contribute to increased heart disease risk associated with ETS exposure.

The significance of this report is highly questionable. Very few details are available -- not even the ages of the people studied are given in the abstract. In addition, the relationship, of any, of vitamin levels to subsequent heart disease is not scientifically established. Furthermore, even the authors acknowledge that their data on plasma vitamin C may at least in part be a result of different levels of dietary intake, rather than any direct effect of ETS exposure.

WLS/tks

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Supplement to Circulation

Abstracts From the 65th Scientific Sessions
New Orleans Convention Center
New Orleans, Louisiana
November 16-19, 1992

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Subject and author indexes are keyed to abstract numbers, not page numbers. However, all Named and Invited Lectures and all Young Investigator Award/Prize Abstracts are keyed to page numbers within this supplement. Indexes are located at the back of this supplement. All other supplements to this volume of *Circulation* will be indexed in the December issue.

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Reduced Plasma Ascorbic Acid Concentrations in Women Regularly Exposed to Environmental Tobacco Smoke (ETS):
Diane L. Tribble and Stephen P. Fortmann.
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Oxidative processes have been implicated in the pathogenesis of heart disease, offering a potential explanation for the high risk attributable to smoking. Cigarette smoke contains numerous oxidants, and smokers exhibit reduced circulating concentrations of the antioxidant vitamin ascorbic acid (AA), primarily as a result of oxidant-mediated depletion although reduced dietary intake also has been noted. We measured plasma AA concentrations and dietary AA intake in non-smoking women exposed to ≥ 20 hr/wk ETS, i.e., passive smokers (PS), as compared with nonsmokers with ≤ 2 hrs ETS exposure/wk (NS) and active smokers (AS), to assess whether PS also may exhibit suboptimal AA nutrition. Plasma AA was measured by HPLC with electrochemical detection, and dietary and vitamin supplement AA intakes were assessed using a semi-quantitative food frequency questionnaire.

Results:	NS(n=46)	PS(n=27)	AS(n=33)
Cigs/d	0	0	24.5 \pm 5.4**
ETS exposure (hr/wk)	0.2 \pm 0.6	35.3 \pm 12.9**	20.7 \pm 20.4**
Plasma AA (μ M)	69.4 \pm 21.3	51.9 \pm 23.3**	42.3 \pm 20.2**
Dietary AA (mg/d)	129.8 \pm 79.1	117.4 \pm 56.2*	129.8 \pm 79.1
Sumol AA (mg/d)	152.0 \pm 254.9	207.5 \pm 289.5	184.4 \pm 311.6

NS vs. PS or AS: *p<.05; **p<.001; PS vs. AS: †p<.001.

Both PS and AS exhibited reduced plasma AA relative to NS. One (-2%) NS, 4 (-15%) PS, and 6 (-18%) AS exhibited hypovitaminosis C (plasma AA<23 μ M). Reduced plasma AA in PS may be partially due to reduced dietary AA. These results suggest that suboptimal AA nutrition may contribute to increased heart disease risk associated with ETS exposure.

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GREEN, M.S., SHAHAM, J., GREEN, J., HARARI, G. AND BERNHEIM, J.,
"ASSOCIATION OF PASSIVE SMOKING WITH INCREASED CORONARY HEART
DISEASE RISK IS NOT EXPLAINED BY ELEVATION OF LEUCOCYTE COUNT,"
EUROPEAN JOURNAL OF PUBLIC HEALTH 3(1): 14-17, 1993.

Some previous research involving active cigarette smokers has reported that smokers may have higher numbers of leukocytes (white blood cells) than nonsmokers. It has been speculated that these higher leukocyte counts may be one mechanism whereby smoking might increase heart disease risk. Green, et al. (1993) addressed the question of whether ETS-exposed nonsmokers might also show increased leukocyte counts.

Green, et al. examined a group of 250 male factory workers. These men were questioned regarding their smoking habits and their reported exposure to ETS in the workplace and at home. Urine samples were also collected for cotinine analysis. Green, et al. reported that, on the average, smokers had higher leukocyte counts compared with nonsmokers. However, based both on reported ETS exposure as well as on cotinine data, exposure to ETS was not associated with increased leukocyte counts. The authors concluded that, if ETS exposure is associated with increased heart disease risk, it is not mediated through an effect on leukocyte count.

These findings suggest that any association of passive smoking with coronary heart disease is not through an elevation of leucocyte count.
(Abstract, p. 14)

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Association of passive smoking with increased coronary heart disease risk is not explained by elevation of leucocyte count

M. S. GREEN, J. SHAHAM, J. GREEN, G. HARARI, J. BERNHEIM*

The increased risk of coronary heart disease in cigarette smokers may be due at least partly to an elevation of the leucocyte count. Chronic passive smoking has also been found to be associated with an increased risk of coronary heart disease, but its effect on the leucocyte count has not been reported. In this study 250 male factory employees aged 20-64 years were interviewed on smoking behaviour and exposure to environmental tobacco smoke, and blood counts were determined. Urinary cotinine was measured by radio-immunoassay and corrected for urinary creatinine concentrations. Mean leucocyte count was significantly higher among smokers compared with non-smokers (8,666 compared to 6,900; $p < 0.001$). On the basis of smoking history, passive smokers had leucocyte counts similar to non-smokers. These findings were confirmed when leucocyte counts were compared with urine cotinine to creatinine ratios. The association of haematocrit and haemoglobin with smoking was similar to that of leucocyte count. These findings suggest that any association of passive smoking with coronary heart disease is not through an elevation of leucocyte count.

Key words: smoking, passive smoking, urine cotinine, blood count, leucocytes, coronary heart disease

Leucocyte count has been shown to be independently associated with an increased risk of coronary heart disease (Friedman et al. 1974; Zolotar et al. 1981; Kostis et al. 1984; Ernst et al. 1987). In addition, cigarette smokers tend to have higher leucocyte counts than non-smokers (Pettit & Kipp 1986; Green et al. 1992) and it has been suggested that this may be one of the mechanisms by which smoking increases the risk of coronary heart disease (Kostis et al. 1984; Ernst et al. 1987). Exposure to environmental tobacco smoke (passive smoking) has also been shown to be associated with coronary heart disease (Garland et al. 1985; Glantz & Parmley 1991), although the mechanism of this association is not clear. Toxic agents have been demonstrated in both mainstream cigarette smoke (smoke inhaled and exhaled by the smoker) and side-stream cigarette smoke (emitted from the burning zone) (Hoffman & Hoffman 1987; Erikson et al. 1988). There is some evidence that enzyme systems responsible for the detoxification of smoke constituents are not induced to the same extent in passive smokers as in active smokers (Hoffman & Hoffman 1987; Erikson et al. 1988). In a recent study, three hours of heavy exposure of 16 non-smokers to environmental tobacco smoke produced a mean increase of 33 per cent in leucocyte count (Anderson et al. 1991). However, to the best of our knowledge there are no reports on whether chronic passive exposure

to environmental tobacco smoke is reflected in an elevation of the leucocyte count.

Self-reported exposure to environmental tobacco smoke may only be a crude estimate of actual exposure. Since nicotine in the blood has a short half-life of about two hours (Curvall et al. 1990) it is not suitable as a measure of chronic exposure. On the other hand, cotinine, the major metabolite of nicotine, is specific to tobacco and is concentrated and excreted in the urine and saliva (Curvall et al. 1990). It has a half-life of about 19 hours in the blood and it has been shown that the urinary cotinine level is a sensitive measure of daily exposure to tobacco smoke (Wald et al. 1984; Waller et al. 1988; Cummings et al. 1990).

The aim of this study was to compare the leucocyte count in cigarette smokers with that of non-smokers exposed to varying concentrations of environmental tobacco smoke. Urinary cotinine concentrations were used to determine the extent of exposure to environmental tobacco smoke. While the emphasis in this study was to evaluate the association of exposure to tobacco smoke and leucocyte count, haematocrit per cent and haemoglobin concentration are also analyzed for the sake of comparison.

METHODS

Subjects

Three hundred seventy-five men aged 20-64 and employed in a single industrial worksite (93% were blue-collar workers) underwent routine health screening carried out by staff from our institute. Participation was voluntary and the examinations were offered free of charge. The response rate for participation in the study was almost 100%.

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per cent. A random sample of 250 were included in a special study of passive smoking. The subjects were all interviewed by the same trained interviewer, using a questionnaire on current smoking habits, exposure to tobacco in the workplace and exposure to tobacco smoke at home. A typical question was structured as follows: Do your co-workers smoke in your work area? 1) Not at all; 2) Infrequently; 3) Frequently; 4) Most of the time. Answers 2, 3 and 4 correspond to the classification of mild, moderate and extensive exposure to tobacco smoke. Four groups were defined: a) Active smokers (categorized by <10, 10–20 and >20 cigarettes per day); b) non-smokers reporting minimal exposure to tobacco smoke both in the workplace and at home; c) non-smokers reporting moderate exposure to tobacco smoke of others in the workplace or at home; and d) non-smokers reporting extensive exposure to tobacco smoke of others in the workplace or at home. Subjects were asked to provide urine samples during a regular workday, between 12:00 p.m. and 2:00 p.m. Aliquots of 1.5 ml were kept in serum storage tubes (screw top) at -70°C until tested.

Urinary cotinine and creatinine measurements

Urinary cotinine concentrations were determined in the nephrology research laboratory at Meir General Hospital, using radio-immunoassay (RIA) (Double Antibody Nicotine Metabolite, Diagnostic Products Corporation, Los Angeles). Quality control was monitored by means of control standards which were included with the test kit and control urines which were stored at -20°C . Since it was not possible to obtain 24-hour urine samples, urinary creatinine was determined using standard methods on an automatic analyzer in order to correct for the cotinine concentrations in random urine specimens. The cotinine results (in ng/ml) were expressed relative to the urinary creatinine concentrations (mg/dl), a method used successfully by other investigators (Wall et al. 1988, Cummings et al. 1990).

Statistical analyses

The mean cotinine concentrations, cotinine to creatinine ratios and blood counts for each of the subgroups identified by the questionnaire were compared by one-way analysis of variance and Duncan's multiple range test. The mean blood counts were compared graphically for different intervals of cotinine:creatinine ratios and tested for trend by means of linear regression. In addition, the association between blood counts and the cotinine:creatinine ratios were examined using non-linear regression.

RESULTS

Some degree of passive exposure to tobacco smoke at work was reported by 85.6 per cent, whereas only 27.3 per cent reported any such exposure at home. Urinary cotinine concentrations and cotinine to creatinine ratios are shown by smoking status in table 1. The cotinine:creatinine ratios distinguish between four distinct groups based on self-reported exposure to tobacco smoke: minimal or moderate passive exposure, heavy passive exposure or smoking less than 10 cigarettes per day, smoking 10–20 cigarettes per day, and smoking more than 20 cigarettes per day. Nevertheless, there was overlapping of the ranges of cotinine to creatinine ratios between the self-reported categories, suggesting either in-accuracy of self-reporting, or variation in nicotine absorption or metabolism, or both. Results for the comparison of the blood parameters in the different sub-groups classified by reported smoking or exposure to tobacco smoke are shown in table 2. Those smoking more than 10 cigarettes per day had a significantly higher mean leucocyte count than the light smokers or non-smokers regardless of the degree of passive exposure to tobacco smoke. Haematocrit and haemoglobin showed a similar pattern.

The mean blood counts by different intervals of the cotinine to creatinine ratio are shown in the figure. While the linear trends were significant in all three, the counts were clearly elevated only at levels of the cotinine to creatinine ratio consistent with heavy smokers and much higher than those seen in non-smokers exposed to envi-

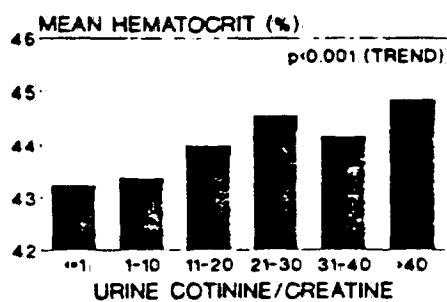
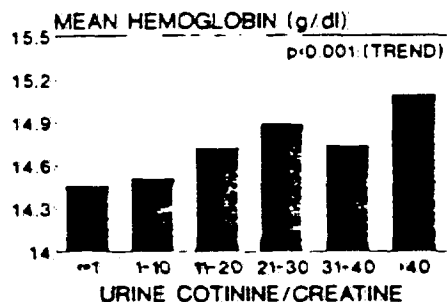
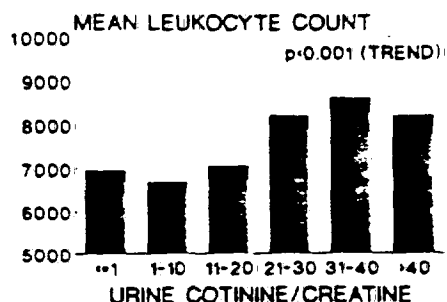
Table 1 Mean (\pm standard deviation) urinary cotinine and cotinine:creatinine ratios, by smoking status (minimum and maximum given in parentheses).

Smoking status	n	Urinary markers			Cotinine:creatinine ratio		
		Cotinine concentration (ng/ml)			Cotinine:creatinine ratio		
		Mean	SD	Range	Mean	SD	Range
Non-smokers							
None or minimal passive exposure	60	36.3 ^a	36.2	0–175	0.3 ^a	0.3	0–1.2
Moderate passive exposure	64	154.3 ^b	473.2	0–2,644	0.9 ^a	2.7	0–14.2
Heavy passive exposure	22	1,074.1 ^b	2,745.7	0–10,593	10.4 ^b	25.6	0–93.7
Smokers							
< 10 cigarettes per day	27	2,100.8 ^b	2,327.6	45–8,522	12.9 ^b	11.6	0.5–42.0
11–20 cigarettes per day	42	7,242.3 ^c	5,277.7	458–22,299	38.1 ^c	20.1	2.7–99.3
≥ 20 cigarettes per day	35	7,853.3 ^c	3,864.4	85–22,036	44.6 ^d	16.9	0.6–62.6
F _{3,249} (one-way analysis of variance)		65.7			85.9		
P		< 0.0001			< 0.0001		

^{a, b, c, d} Indicate significantly different groups by Duncan's multiple range test at the 5 per cent level of significance.

Table 2 Mean leucocyte count, haematocrit and haemoglobin by smoking status (95% confidence interval in parentheses)^a

Smoking status	n	Leucocyte count (x1,000)	Blood parameters			
			Haematocrit	Haemoglobin (g/100 ml)		
Non-smokers						
None or minimal passive exposure	60	6.90 (6.52-7.23) ^a	43.6 (42.9-44.3) ^a	14.6 (14.4-14.8) ^a		
Moderate passive exposure	64	7.03 (6.64-7.41) ^a	43.1 (42.6-43.5) ^a	14.4 (14.2-14.5) ^a		
Heavy passive exposure	22	6.76 (6.15-7.36) ^a	43.4 (42.3-44.5) ^a	14.5 (14.0-14.9) ^a		
Smokers						
< 10 cigarettes per day	27	7.13 (6.66-7.66) ^a	43.4 (42.5-44.2) ^a	14.5 (14.0-14.8) ^a		
11-20 cigarettes per day	42	6.00 (5.34-6.63) ^b	44.5 (43.7-45.2) ^b	14.9 (14.6-15.2) ^b		
≥ 20 cigarettes per day	35	8.66 (8.01-9.24) ^b	44.6 (43.6-45.6) ^b	15.0 (14.7-15.4) ^b		
F-test (one-way analysis of variance)		7.8	3.2	3.4		
P		< 0.001	0.000	0.005		

^a Indicate significantly different groups by Duncan's multiple range test at the 5 percent level of significance

16 Figure Mean leucocyte count, hematocrit ratio and hemoglobin by intervals of the urinary cotinine to creatinine ratio

ronmental smoke. Non-linear regression of the blood counts on the cotinine to creatinine ratio yielded a highly significant second degree polynomial term, confirming this observation (detailed analyses not shown).

DISCUSSION

These findings demonstrate that leucocyte count is not significantly elevated in non-smokers exposed to different levels of environmental tobacco smoke. In addition, among light smokers there was no increase in leucocyte count. This suggests that if in fact elevation of the leucocyte count contributes to the risk of coronary heart disease in smokers, this is not likely to be the mechanism for passive smokers or indeed for light smokers. In general the mechanism for the increased risk of coronary heart disease in passive smokers is not well understood. It has been postulated that it may be due to effects on blood factors such as platelet aggregation or through a role of the damaging and mutagenic effects of agents such as the polycyclic aromatic hydrocarbons (PAH) on the endothelial and smooth muscle cells (Giantz & Parmley 1991). In addition, extensive exposure to environmental tobacco smoke may result in reduced oxygen supply to the myocardium (Giantz & Parmley 1991).

It has been suggested that the elevation of the white cell count in smokers results from a chronic inflammatory response in the bronchi of regular smokers (Petitti & Kipp 1986). Toxic products in cigarette smoke such as tar and cadmium may be responsible for this effect (Lewis et al. 1972). Despite the fact that cigarette smoking has an acute effect on the leucocyte count (Friedman et al. 1973), this effect persists for some time after quitting (Petitti et al. 1986). This may be due at least in part to changes in hormonal levels resulting from smoking which in turn might affect the leucocyte count (Petitti & Kipp 1986).

The findings in this study suggest that at the population level, at least among adult men, chronic exposure to environmental tobacco smoke has little or no effect on leucocyte count. The relatively narrow confidence intervals for the leucocyte counts suggest that even if the study

was performed on a larger sample, the results would be largely unchanged. Despite this finding, an effect in some heavily exposed individuals cannot be excluded. It should be mentioned that most of the subjects were blue-collar workers, although there is no obvious reason to predict different findings for white-collar workers. The possibility that passive smoking may have some effect on subfractions of leucocytes cannot be excluded (Anderson et al. 1991). Nevertheless, the results of the present study indicate that the mechanism underlying the increased risk of coronary heart disease in passive smokers is not through elevation of leucocyte count.

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